21

Cancers

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Human cancer consists of more than 100 distinct diseases, each defined by its anatomic site of origin and microscopic features (cell type). The two characteristics shared by all cancers are the uncontrolled proliferation of cells and their invasion into other tissues. Cancers differ, however, in their clinical features. Some, such as esophageal cancer, progress rapidly, are relatively intractable to treatment, and are almost uniformly fatal. Others, chronic lymphocytic leukemia, for example, usually follow an indolent course and may persist for decades with little morbidity.

Cancers differ also in their etiology. As a consequence, individual cancer types tend to have distinct epidemiological features, preferentially affecting particular populations as defined by geography, culture, and personal habits. For example, cervical cancer occurs more often in the developing world and among women with low income and a history of many pregnancies. In contrast, breast cancer tends to strike more affluent women who live in industrial countries and have a history of fewer or no pregnancies (Kelsey and Hildreth 1983).

An analysis of the health policy implications of cancer can therefore not proceed very far using an aggregate concept of cancer because aggregation obscures important details of cause and potential interventions. Two countries can have the same aggregate rate of occurrence of cancer but need to employ very different types of intervention. The discussion that follows uses a level of disaggregation that distinguishes the ten most important cancers in the developing world and considers their individual etiological and clinical characteristics.

The focus of this chapter is the implications of cancer epidemiology for health policy in developing countries. A common notion is that cancer is primarily a disease of industrial countries, occurring late in life as a consequence of affluent lifestyle. It thus is felt to be not important in developing countries, where the focus should be on infectious diseases and childhood. There are good reasons why cancer deserves attention, however. First, several important cancers, including stomach and liver cancer, occur most often in poorer countries (Stjernsward and others 1985; Parkin, Laara, and Muir 1988). Second, some low-income and middle-income countries, such as China, Sri Lanka, Malaysia, and Brazil, have reduced fertility and causes of infant and childhood death, and the relative importance of cancer has increased as the age structure of the population has changed (see, for example, Bumgarner 1992). Third, once an individual is past the hurdle of childhood diseases, cancer looms as one of the three largest causes of death (the other two being accidents and cardiovascular diseases) even in the lowest-income countries of Africa and Asia (Stjernsward and others 1985). Last, changing demographics and increasing tobacco consumption virtually ensure that an epidemic of lung cancer will occur in many developing countries during the next century (Stanley 1986). It is important to act now to prevent tobacco use rather than to wait until the epidemic is manifest.

Despite its importance in adult mortality, cancer has not been considered in shaping health policy in most developing countries. The discussion that follows provides a brief survey of the epidemiology of cancer and gives suggestions for incorporating cancer planning in health policy. The appendix provides a review of the salient characteristics of ten of the most important cancers and the environmental, behavioral, physiological, and occupational circumstances—collectively referred to as risk factors—that have been associated with their occurrence.

Public Health Importance

Accurate information on cancer occurrence (mortality and incidence rates) and on the prevalence of risk factors is essential in assessing the public health importance of cancer and in planning control strategies.

Data Sources

Determination of cancer mortality rates primarily requires a reliable system of death registration and accurate demographic data and thus can be accomplished within the context of mortality measurement for other diseases. Determination of cancer incidence is best achieved through specialized tumor registries (Waterhouse and others 1976). These require an effort directed toward cancer, and in their absence cancer incidence may be approximated by applying estimated case-fatality rates to cancer mortality data (Parkin, Laara, and Muir

1988). The prevalence of risk factors is measured by surveys employing questionnaires or by direct measurement of physical and biochemical characteristics.

Countries vary greatly in the availability and reliability of their cancer data (Muir and Nectoux 1982). This fact largely reflects the limited resources devoted to the measurement of vital statistics by many governments in the developing world. Also, the reliability of cancer data depends on coding practices (Percy and Muir 1989), on the level of medical care, and on the availability and quality of diagnostic procedures. Cancer incidence and mortality rates are likely to be underestimated in countries in which people have little access to high-technology medical care. Although some excellent tumor registries have been established in several low-income countries (Muir and others 1988), they cover cancer incidence in only a minor fraction of the developing world. There also are large gaps in the international data on cancer mortality rates (Kurihara, Aoki, and Tominaga 1984). Thus, the incidence and mortality rates quoted here must be interpreted with the realization that there are severe deficiencies in cancer data.

Global Epidemiology

Cancer accounts for approximately 8.5 percent of the 51 million deaths occurring in the world each year (Hakulinen and others 1986). Of the estimated 4.3 million cancer deaths, more than half (2.5 million) occur in developing countries. In relation to other causes of death, however, cancer seems less important in these countries, in which it accounts for approximately 5.5 percent of all deaths, well below those due to infections (40 percent), circulatory diseases (19 percent), and perinatal events (8 percent). In most industrial countries cancer accounts for approximately 20 percent of deaths, second only to circulatory diseases (about 50 to 55 percent).

There are four principal reasons for the relatively lower importance of cancer as a cause of death in developing countries. One is the continued high death toll from infectious and parasitic conditions that have been largely eliminated as causes of death in the industrial countries. A second reason is that the age structure of the populations of most developing countries is heavily weighted toward young children. Cancer occurs most frequently among older adults, and this group accounts for a small percentage of the populations of these countries. The third reason is that aggregate cancer risks are truly lower in many (though not all) developing countries. Among countries such as Cuba and Costa Rica, age-adjusted cancer mortality rates are approximately one-third to two-thirds less than in typical heavily industrialized countries (Kurihara, Aoki, and Tominaga 1984). Many of these differences, however, are accounted for by lower rates of lung cancer and other tobacco-associated cancers, and the picture is complicated considerably when we consider other cancers, such as those of the stomach and liver. Last, cancers are more likely to be unrecognized in populations with less access to advanced diagnostic facilities, so the actual effect of cancer is underestimated.

In the near future, cancer will become increasingly important in developing countries. Improved sanitation and immunization should lead to better control of infectious diseases, decreasing deaths from these causes. Declining fertility and reduced infant and childhood mortality will eventually shift population age structures from a pyramidal to a more columnar pattern (with a greater proportion of older adults, whose risk of cancer is higher). In addition, tobacco use is increasing in many developing countries, and increases in cancer will undoubtedly follow (Crofton 1984; Stanley 1986).

The pattern of cancer occurrence now differs greatly between developing and industrial countries. In industrial countries, most cancer deaths are due to tumors of the lung, colorectum, breast, prostate, and pancreas. In developing countries the main causes of cancer death are tumors of the stomach, esophagus, lung, liver, and cervix (Parkin, Laara, and Muir 1988). In table 21-1 we provide estimates of numbers of deaths and new cases for the ten most frequent cancers in developing countries.[1] Note that the relative importance of these cancers differs depending on whether one focuses on deaths or new cases. This is because cancers of the lung, stomach, and esophagus are almost invariably fatal, whereas prolonged survival and cure are common for breast, oral, and cervical cancer cases.

The degree of industrial development is an unreliable guide to the pattern of cancer occurrence in a given country. For example, although esophageal cancer is generally more frequent in developing countries, its incidence is also high in northwestern France and parts of eastern Europe (Ghadirian, Thouez, and Simard 1988). Similarly, stomach cancer is common not only in developing countries but also in Japan, where it is the leading cause of cancer death (Kurihara, Aoki, and Tominaga 1984). The occurrence of most cancers actually appears to be determined by factors (such as tobacco consumption, diet, and reproductive practices) that are related only indirectly to industrial development (Doll and Peto 1981).

Accordingly, statements about the cause and prevention of cancer in the developing world (considered as a whole) may not be applicable to all developing countries. Policies to address the cancer problem must be formulated on a country-by-

Table 21-1. Estimated Annual Deaths and New Cases of Ten Most Important Cancers in the Developing World, 1980
(thousands)

Site or type of cancer	*Deaths*	*New cases*
Stomach	280	336
Esophagus	231	254
Lung	187	206
Liver	174	192
Cervix	154	370
Colon/rectum	108	183
Mouth/pharynx	101	272
Breast	97	224
Lymphoma	81	122
Leukemia	81	106

Note: Excludes skin cancers.
Source: Parkin, Laara, and Muir 1988.

country basis, taking into account particular features of cancer occurrence and the prevalence of particular risk factors in each population. Clearly, reliable country-specific data will be crucial to this process.

Time Trends in Cancer Occurrence

There is relatively little information on cancer trends in developing countries themselves, and one must try to draw parallels from industrial countries that have a longer history of collecting cancer incidence and mortality data. Over the past fifty years, the most striking changes in cancer occurrence in many of these countries have been increasing rates of lung cancer and falling rates of cancers of the stomach and uterine cervix (Kurihara, Aoki, and Tominaga 1984; Stanley, Stjernsward, and Koroltchouk 1988). The profound increase in lung cancer is almost entirely attributable to tobacco use, which became prevalent (in the United States and western Europe) early in this century (Doll and Peto 1981). There has also been a smaller increase in other tumors, such as bladder cancer, that are related to tobacco use but not as strongly as is lung cancer. The fall in uterine cervical cancer deaths is not fully understood (Knox 1982). Possible contributing factors, besides Pap testing, include changes in sexual practices, improved genital hygiene, and increased frequency of hysterectomy (removing the uterus removes the risk of cervical cancer). Reasons for declines in stomach cancer mortality in developing countries are uncertain (Stanley, Stjernsward, and Koroltchouk 1988). A plausible explanation is that diets have improved and consumption of spoiled or mold-contaminated food (due to better food storage and refrigeration) is thus lower (Bjelke 1982). Also, increased consumption of antioxidants (as food additives and vitamin C) may have contributed to the decline. Lastly, reduced rates of infection with *Helicobacter pylori*, a pathogenic bacterium implicated in gastric carcinogenesis, may have resulted from better sanitation in industrial countries (Correa 1992).

Within the industrial countries there has been little change during the last several decades in deaths due to cancers of the breast (Stanley, Stjernsward, and Koroltchouk 1988) and colon (Boyle, Zaridze, and Smans 1985). Reported increases in some countries of breast cancer and pancreatic cancer are difficult to interpret because there have been improvements in diagnostic capabilities and greater efforts to find cancer, particularly among the elderly. A modest decline in large bowel cancer mortality in some industrial countries also cannot be easily explained, although dietary changes (Boyle, Zaridze, and Smans 1985) or earlier diagnosis and improved treatment may be partly responsible.

In North America and western Europe, mortality from childhood leukemia and lymphoma has fallen dramatically. This observation is attributable to improved treatment methods developed during the past thirty years through a massive investment in cancer research (Miller and Mckay 1984). In countries such as the United States, however, decreases in cancer deaths achieved by improved treatment of leukemia, lymphoma, and other, uncommon, cancers have been offset by increases in deaths from tobacco-associated cancers (Bailar and Smith 1986). These latter cancer deaths are occurring as a result of tobacco smoking initiated decades in the past.

Will these changes be repeated in the developing countries? Tobacco-associated cancers are certain to increase in countries where tobacco use has risen. Cancers of the breast and colorectum are also likely to increase in populations that adopt the reproductive patterns and diet of more industrialized countries. A drop in the occurrence of stomach cancer seems likely in countries in which diets have come to include more fresh fruits and vegetables and fewer spoiled foods. Changes in sexual practices may lead to declines in cervical cancer. Changes in health care and hygienic practices could lead to a reduction in hepatitis and, hence, liver cancer. In the absence of direct intervention, however, these favorable changes are apt to occur gradually, and increases in lung, colorectal, and breast cancer may offset declines in stomach, liver, and cervical cancer.

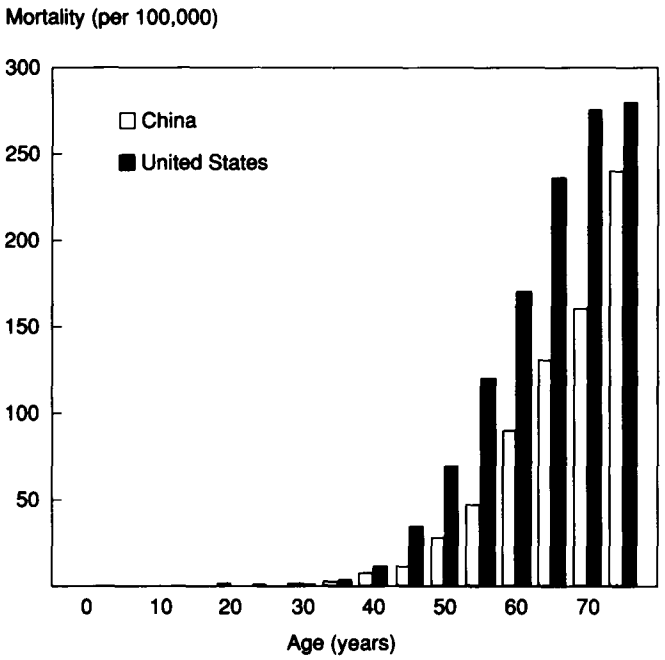
The Current Burden of Cancer

The total economic cost of cancer to society can be conveniently partitioned into indirect and direct costs. The indirect cost is the cost to society from the loss of productive life, and the direct cost is the value of the resources (including those used for health sector services) required by cancer. The proportional split of total cost between these two categories varies considerably by disease. In a study by Rice, Hodgson, and Kopstein (1985) of the cost of disease in the United States for 1980, direct costs for cancer were only 26 percent of total cost, and the remainder was composed of the indirect costs of morbidity (11 percent) and mortality (63 percent). Only injuries, at 23 percent, had direct costs that were a lower percentage of the total. For comparison, the direct costs of diseases of the genitourinary system were 80 percent. The importance of indirect costs of cancer is attributable to the high case-fatality rates for cancers and the fact that in the developing countries cancer primarily affects people during their productive years (albeit often relatively late in life).

Although morbidity and mortality rates, and therefore the total costs of cancer, vary considerably on a global basis, with a few exceptions, the parameters determining the proportional importance of indirect cost per case do not vary markedly between countries. In figures 21-1, 21-2, and 21-3, respectively, we show the age-specific mortality rates for lung cancer, liver cancer, and stomach cancer in China and the United States. As for most cancer, the force of mortality is highest late in life. Leukemia (shown in figure 21-4) is a notable exception, with appreciable mortality occurring earlier in life.

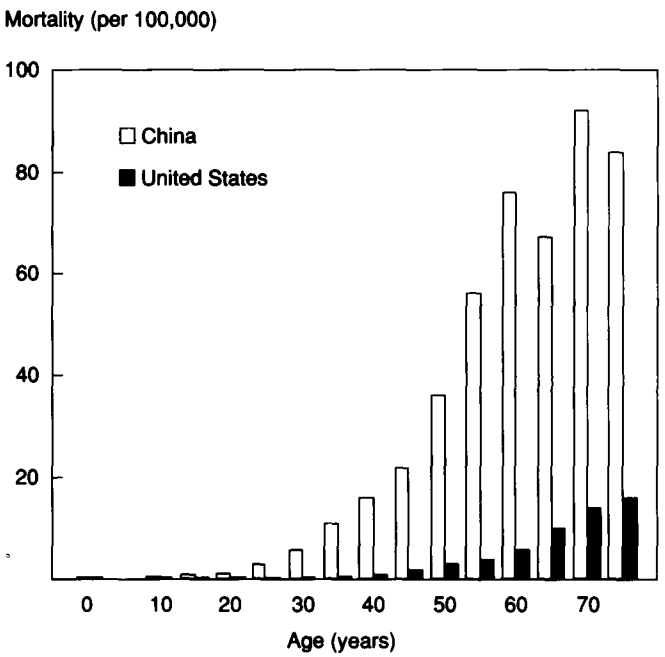
A general measure of the burden of specific cancers is given by calculation of years of life lost (YLL), measured as the difference between the age of death for victims of the disease in comparison with life expectancy. In table 21-2 we give the average YLL per case and the total number of years lost out of a population of 1 million for eight main cancers in a prototypical developing country. In order of total burden, cervical, breast, and stomach cancers are the most important for women, and

Figure 21-1. Age-Specific Mortality for Cancer in China and the United States



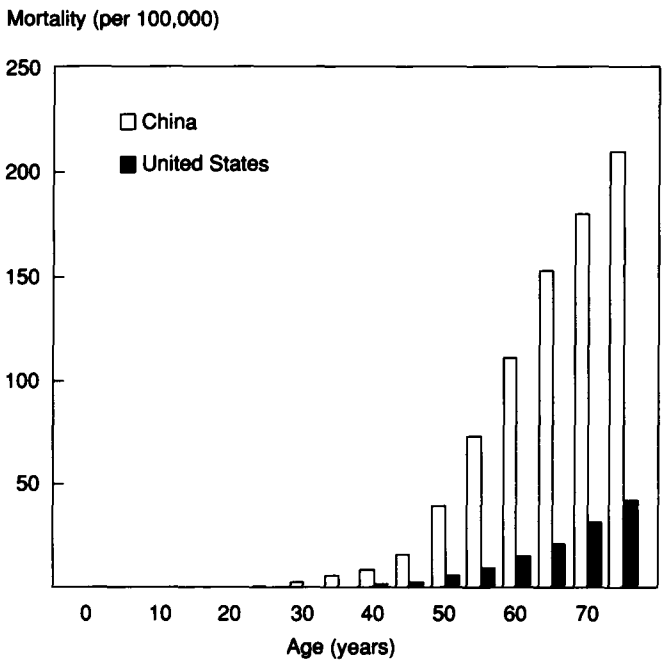
Source: China: unpublished Disease Surveillance Point data 1986; U.S.: National Institutes of Health 1988.

Figure 21-2. Age-Specific Mortality for Liver Cancer in China and the United States



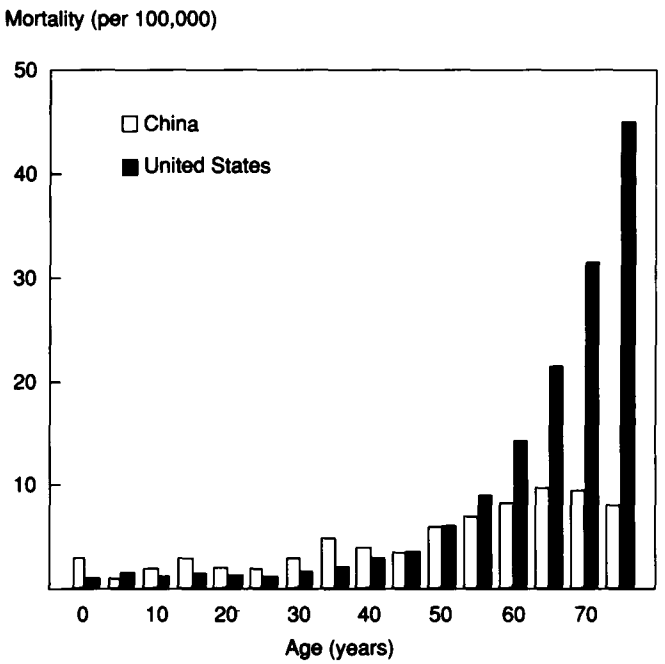
Source: China: unpublished Disease Surveillance Point data 1986; U.S.: National Institutes of Health 1988.

Figure 21-3. Age-Specific Mortality for Stomach Cancer in China and the United States



Source: China: unpublished Disease Surveillance Point data 1986; U.S.: National Institutes of Health 1988.

Figure 21-4. Age-Specific Mortality for Leukemia in China and the United States



Source: China: unpublished Disease Surveillance Point data 1986; U.S.: National Institutes of Health 1988.

Table 21-2. Average Years of Life Lost from Premature Mortality from Cancer in Developing Countries

Site or type of cancer	Average age at death		Average years of life lost per death		Years of life lost per million population[a]		
	Male	Female	Male	Female	Male	Female	Total
Stomach	64	62	16	18	853	561	1,414
Liver	56	57	22	22	814	312	1,126
Esophagus	65	65	16	16	714	402	1,116
Leukemia	32	34	42	41	599	418	1,016
Lung	63	66	17	15	721	210	931
Cervix	n.a.	61	n.a.	18	n.a.	837	837
Colon/rectum	61	60	18	20	313	304	617
Breast	n.a.	57	n.a.	22	n.a.	645	645
Total	59	58	20	21	6,611	5,906	12,517

n.a. Not applicable.
a. Based on population distribution, incidence, and case-fatality rates.
Source: Parkin, Laara, and Muir 1988.

stomach, liver, lung, and esophageal cancers are of primary concern for men.

Prevention

A large number of primary and secondary prevention activities have been proposed for control of cancer mortality. These activities vary greatly, however, in their cost and potential effectiveness as part of a national cancer strategy. A considerable literature has emerged that discusses causes of cancer and the effectiveness, hazards, and (to a regrettably lesser extent) the costs of preventive activities. Most of this literature has been oriented toward industrial countries, but some general conclusions apply in the developing world. In the next two subsections we discuss the implications of current knowledge of cancer risks for primary and secondary prevention programs in developing countries.

Primary Prevention

Primary preventive activities are designed to lessen exposure to risk factors. The main potential risk factors identified for intervention include tobacco consumption, food, alcohol, infections, environmental and occupational chemicals, and radiation (Doll and Peto 1981). Evaluation of the potential usefulness of alternative interventions has several components: (a) the importance of targeted cancers and the prevalence of targeted risk factors in individual countries must be established by surveillance; (b) the technical effectiveness of specific interventions is being explored in experiments in industrial countries, but little is known about the ease of transferring the results of these experiments to other countries; (c) the feasibility of preventive activities, even though they may be technically effective, is impeded by the practical difficulty of altering underlying behavior and customs, interfering in production or consumption processes, and managing large-scale preventive campaigns; and (d) prevention activities must compete with other resource uses, and the cost of the activities is an important determinant of their competitiveness. Thus, the relative potential of preventive interventions is dependent on the ranking of the targeted cancer as a cause of lost life and economic productivity, the technical effectiveness of the intervention, the feasibility of implementing the primary prevention activity, and the cost per person covered by the activity. These factors are considered in the specific interventions discussed below.

PROGRAMS TO REDUCE TOBACCO CONSUMPTION. A clear causal relationship is established between tobacco consumption and many cancers, including tumors of the lung, mouth, upper respiratory and digestive tracts, kidney and urinary tract, and other sites, with the most important link being to lung cancer (USDHHS 1982; IARC 1986). The many cancer deaths attributable to tobacco consumption mark antitobacco programs for special consideration among cancer prevention activities. In Europe and North America the dramatic increase in lung cancer in the last thirty years has made it the leading cause of cancer mortality and one of the main causes of death. The increase has been firmly linked to earlier changes in smoking behavior. Because of formerly low levels of cigarette consumption, lung cancer has been a relatively less important cause of death in developing countries, but as life expectancy and smoking prevalence increase, lung cancer and other smoking-related causes of death are becoming more important. Additionally, chewing tobacco, especially betel nut chewing in India, has long been an important cause of oral cancer (WHO 1984).

Studies of the hazards of tobacco consumption have included examinations of the difference in risk for alternative forms of consumption (cigarettes, pipes, cigar), dose (daily number of cigarettes, tar and nicotine content, and method of ingestion), and duration (age started or years of habit [Peto 1986]). The risk of lung cancer for those who smoke approximately one to ten cigarettes per day is three to five times greater than for nonsmokers; for those who smoke one pack (twenty cigarettes) the relative risk is seven to nine times greater; and

for two packs, nine to twenty-five times greater. Smokers who report that they do not inhale nevertheless have a risk four to eight times that of nonsmokers.

A striking aspect of the link between smoking and cancer is that duration of smoking appears to be more important than daily dose in determining lung cancer risk. For example, in one summary of the literature the author concludes that "a three-fold increase in the daily dose-rate may produce only about a three-fold increase in effect, while a three-fold increase in duration might produce about a 100-fold increase in effect" (Peto 1986 p. 23). The effect of duration of the smoking habit on lung cancer is crucial in assessing past trends of cancer in industrial countries and in projecting the future effect of cancer in developing countries. Current high rates of lung cancer in industrial countries result from a high percentage of the population that started smoking at an early age and continued to smoke for several decades. Cultural and social changes in developing countries are lowering the starting age for smoking, increasing the duration of smoking, and increasing the percentage of the population that smokes.

Tobacco consumption is increasing in developing countries at the same time that it is leveling off or decreasing in the industrial world (Crofton 1984). Between 1980 and 1986, consumption increased at an average of 5.4 percent per year in developing countries. The percentage of the population that smokes is higher in many developing countries, but per capita consumption tends to be greater in higher-income countries (IARC 1986). Rising per capita income, however, is expected to increase per capita tobacco consumption, and this effect is greater for lower-income countries. A 10 percent increase in per capita income can be expected to create a 7 percent increase in tobacco consumption in middle-income countries and more than a 13 percent increase in lower-income countries.[2] Thus, it is clear that, unless preventive measures are taken, tobacco consumption will continue to increase as development proceeds in developing countries.

Although the current pool of smokers will inevitably generate more lung cancer in the future, even greater increases can be avoided by preventing starts. Possible components for prevention programs include prohibiting cigarette advertising, requiring warning labels on cigarette packages, using antismoking advertising, instituting educational programs in schools and in work groups, banning tobacco smoke from workplaces and public areas, increasing the price of tobacco products through special taxes, and finally (with limited effectiveness) decreasing the carcinogenic content of cigarette smoke through tobacco processing and filters.

Most of these program components involve behavioral change, so their feasibility is highly dependent on the cultural context in which they are carried out. In addition, the numerous elements in a smoking prevention program require national coordination, monitoring, and motivation (Mackay 1989). The feasibility of an effective program is thus apt to vary considerably across developing countries. Some encouragement can be taken from the moderate success in reducing smoking in the United States during the last twenty years, despite the relatively loose social structure and limited government ability to produce behavioral change. The United States effort has benefited from effective national coordination provided by the Surgeon General's office and the Office of Smoking and Health in the Department of Health and Human Services. Progress has been retarded, however, by agricultural and commercial interests within and outside government. Thus, a full national program to contain tobacco consumption in a given country would also likely involve several ministries directly, notably the education and health ministries, and would need to be coordinated through a special agency or committee to ensure interagency cooperation.

The cost of an antismoking program is difficult to estimate but is probably not great; implementation is more a matter of political and social will than specific costly activities. The primary cost of a basic antismoking education program is that of organizing and supplying an informational effort. An information campaign could include warnings of the adverse health consequences of smoking on cigarette packets; antismoking messages in posters, billboards, newspapers, and on the radio; information dissemination through the health system; and school programs. Cost items would include advertising expense; short-term training courses and seminars for health professionals, teachers, and local leaders; and supervision and management. The cost would be dependent on the available infrastructure for information and education dissemination and on the scale of the program. Some estimate of the cost can be made from examination of other programs that use informational campaigns to bring about behavioral change. On the basis of the cost of training programs and information and education activities in several World Bank projects, the cost per capita could vary between 0.005 and 0.025 percent of the annual gross national product per capita (GNPN) in a typical low-income country.[3]

A particularly important problem for antitobacco programs is that tobacco, because of its nicotine content, produces a strong consumption dependence that must be recognized in prevention strategies. For this reason it seems more feasible, and less costly, to prevent new starts than to convert those who have already developed a dependence.[4] The beneficial effects of an antismoking campaign would be to prevent new smokers from starting, to convert previous smokers to nonsmoking status, to convert some smokers to the use of low-tar cigarettes, and to reduce passive smoking. It is possible to use a few plausible and simple assumptions from available information to demonstrate the low cost per unit of effect in preventing new starters and encouraging smoking cessation in a hypothetical low-mortality population of 1 million.

Out of 1 million people with a smoking prevalence of 0.5 among the adult male population and 0.2 among adult females, the annual number of new starters is estimated to be 8,307 (6,390 men and 1,917 women). Of these, approximately 25 percent will die from causes attributable to smoking, and the average age of death will be fifty-five years, resulting in a premature loss of thirteen years of life for each smoking-induced male death and sixteen years for each female death. The total

Table 21-3. Cost per Year of Life Gained from an Antismoking Campaign, as a Function of Smoking Starts Averted
(percent of per capita GNP)

Program cost per capita (percent GNPN)	Proportion of new smoking starts averted		
	0.10	0.25	0.50
0.005	1.8	0.7	0.4
0.010	3.5	1.4	0.7
0.015	5.3	2.1	1.1
0.020	7.0	2.8	1.4

Note: For a hypothetical program. Information for the United States indicates that 25 percent of smokers will die from smoking-attributed causes (50 percent from coronary, 20 percent from cancer, and 15 percent each from cerebrovascular and pulmonary diseases. When weighted across YLL per death by cause, there is an average of thirteen YLL for men and sixteen YLL for women. The total years of life lost from all smoking starts is 28,435 per million persons in the absence of any intervention program.
Source: Authors.

years of life lost will be 28,000. If a national smoking campaign, costing 0.01 percent GNPN per person could have prevented 50 percent of new starts, the cost per year of life gained (YLG) would have been 0.7 percent GNPN. Obviously, this is a low cost for such a significant benefit.

The cost of an antismoking campaign per YLG is sensitive to the program cost per capita and the efficiency of the program measured as the proportion of new starts averted. In table 21-3 we give the cost-effectiveness of an antismoking campaign under several alternative assumptions. Even under adverse assumptions—a cost per capita of 0.02 percent GNPN and an efficiency of only 0.10 of new starts averted—the program remains relatively inexpensive at only 7 percent GNPN per year of life gained.

It might be argued that, because most effects of the smoking campaign expenditure would not occur until many years after the program expenditure, some adjustment is needed to take account of time. Discounting provides a method of comparing events that occur at different points in time. If we use a discount rate of 3 percent and use the difference between the average age of starting smoking (twenty-one years) and the average age of a smoking death (fifty-five years) as the discount period, the cost per discounted unit of effect is still only 1.9 percent GNPN (table 21-4).[5]

The cost-effectiveness calculations above were made on the assumption that the total effect of the program would be to prevent new starts. There will also be effects in bringing about cessation in response to the basic informational and educational campaign, and these effects, added to prevention of new starts, will increase the cost-effectiveness of the program. Cessation is difficult to achieve but can be cost-effective. Over a ten-year period of sustained informational effort, without any special programs targeted specifically at selected smoker groups, a 10 percent quit rate would be possible in the industrial countries (Altman and others 1987; Warner 1987), and a well-designed program conceivably would be more successful in some developing countries. Compared with preventing new starts, the effects of quitting would be less, however. The relative risk (RR) of mortality from all causes for smokers as opposed to nonsmokers is about 2 on average, and a smoker's chance of dying from a cause attributable to smoking is roughly 0.25. About ten years after cessation the RR falls to about 1.25 and a former smoker's chance of dying from a smoking-related cause falls to about 0.0625. With a program cost of 0.01 percent GNPN and a quit rate of 10 percent over ten program years, the cost per YLG is 0.5 percent GNPN undiscounted or 1.6 discounted at 3 percent.

PRIMARY PREVENTION OF VIRUS-ASSOCIATED CANCERS. Several cancers are associated with viral infections. These include liver cancer, which is an outcome of infection with the hepatitis B

Table 21-4. Cost-Effectiveness of Antismoking Programs

Study	Percent of GNPN per death prevented [a]		Percent of GNPN per year of life gained [a]	
	$ra - 0$	$ra - 0.03$	$ra - 0$	$ra - 0.03$
Hypothetical example in text				
New starters only	9.6	26.3	0.7	1.9
Quitters included	7.5	17.6	0.5	1.6
United States cessation programs [b]				
Smoking cessation classes	11.8	18.4	0.8	1.2
Incentive-based contest	6.5	10.1	0.4	0.6
Self-help antismoking kit	2.1	3.2	0.2	0.3
Eddy [c] cessation program	12.0	18.0	0.8	1.0

Notes: Effects include prevention of excess mortality from lung cancer, other cancers, cardiovascular disease, chronic obstructive lung disease, and other causes; it is not practical to identify cancer as a sole objective.
a. Discount rate.
b. Altman and others 1987 present cost per quitter, which has been converted to deaths prevented using an excess mortality rate of 0.1875 and to years of life gained assuming fourteen years of life lost per smoking-associated death. Discounting assumes that the mean age of quitters is forty-two and the mean age at death is fifty-seven. The figures given are based on the additional cost of the special programs and do not include the cost of the national information program.
c. Based on Eddy 1981. Converted to percent GNPN using U.S. GNPN of $12,800.
Source: Eddy 1981; Altman and others 1987.

virus (HBV); cervical cancer, which is related to the human papilloma virus; and nasopharyngeal cancer and Burkitt's lymphoma, which are both related to the Epstein-Barr virus. Of these, the most immediate interest is in the link between HBV and liver cancer because of the strength of the evidence indicating causality and because of development, during the last fifteen years, of an effective vaccine (WHO 1983; Beasley 1988).

The etiology of HBV infection is complex. The virus is transmitted through close contact with serum-derived fluids, including blood, dental exudates, skin exudates, and semen. Of those who develop infection, the proportion dying within a few months is approximately 0.00125, although a much higher proportion have symptoms of hepatitis. Longer-term consequences of the infection are much more frequent and are associated with development of a chronic carrier state of the virus. From twenty to forty years following HBV infection those with the carrier state are at much greater risk of mortality from both primary liver cancer (PLC) and cirrhosis. The percentage of persons who become chronic virus carriers is closely related to the age of infection; most infected infants develop the carrier state, but fewer than 10 percent of those infected in adulthood become carriers. A study of HBV carriers in Taiwan found that the incidence of PLC among carriers was about 200 times greater than among noncarriers (Beasley and others 1981). Other studies indicate that aflatoxin consumption acts with the HBV carrier state to increase risks of PLC and cirrhosis (Bulatao-Jayme and others 1982;Van Rensburg and others 1985; Yeh and others 1989). The long-term excess risk of mortality from HBV-linked causes is about 15 to 30 per 1,000 cases (ITFH 1988).

There is no standard treatment for HBV infection. Prevention strategies include immunization, better sanitation, and improved sterilization of medical instruments, needles, and syringes. During the last ten years, development of both plasma-derived and recombinant DNA types of vaccine against HBV virus has made it technically possible to prevent infection (Szmuness and others 1981; Francis and others 1982; Wainwright and others 1989). Both types of vaccine are safe and 75 to 95 percent effective, depending on delivery conditions. Until recently the price of vaccine was high (more than $100 for a full course of three shots using the recombinant DNA type of vaccine), but a fall in the price of HBV vaccine to below $1 per injection has increased the possibility of large-scale programs for the control of hepatitis.

The International Task Force on Hepatitis B Immunization (ITFH) distinguishes between areas of low, intermediate, and high HBV prevalence. In areas of low prevalence (western Europe, Australia, North America, and southern South America), 4 to 6 percent of the population show HBV antibodies and only 0.2 to 0.5 percent are carriers; neonatal infection is infrequent. In areas of intermediate prevalence (eastern Europe, countries of the former U.S.S.R., the Mediterranean and the Middle East, Central and South America, and North Africa), 20 to 55 percent of the population show HBV antibodies and 2 to 7 percent are carriers; neonatal infection is frequent. In areas of high prevalence (China, southern Asia, tropical Africa, and the Amazon region of South America), 70 to 95 percent of the population show HBV antibodies and 7 percent to 20 percent are carriers; neonatal infection is frequent. Three-fourths of the world's population live in areas of intermediate or high prevalence. In areas of low prevalence the ITFH recommends that only high-risk groups (such as medical and dental workers) be immunized. In areas of intermediate or high prevalence the most effective preventive strategy is immunization of neonates as part of immediate postnatal care because of the large proportion of infections that are acquired at birth or perinatally.

The feasibility of immunization programs closely parallels that of WHO's Expanded Programme on Immunization (EPI) in general. In countries with a low quality of maternal child health services the obstacles to a correctly timed delivery of the first of the three doses required must be overcome to ensure coverage of the neonatal population. In countries such as China and Indonesia, where development of preventive health services is more advanced, the feasibility of an effective HBV program is high.

Hepatitis immunization can be added to existing EPI programs (The Gambia Hepatitis Study Group 1989), with the additional requirement that, to interrupt transmission, newborn children of infected mothers must be inoculated as soon as possible after birth (usually within seven days). Subsequently, a second dose is to be delivered with EPI vaccines as convenient from four to twelve weeks later, and then a third dose two to twelve months following the second. Two strategies are possible. The first is to immunize all newborns. The second is to screen mothers for hepatitis B surface antigen positivity and immunize only the infants of mothers who were positive (that is, carriers). Because of the cost and current low production of the vaccine, the second strategy is tempting. In low-income countries with high endemicity, however, the first strategy appears preferable. Epidemiological modeling by the ITFH indicates that the screening strategy would not reduce the HBV carrier state by more than 30 to 50 percent compared with a long-run reduction of at least 90 percent for a continued strategy of total newborn vaccination. The capacity for screening and effective follow-up may also be difficult to develop.

Immunization against the hepatitis B virus is a relatively new technology, and the cost has only recently fallen to levels that make it a possible strategy. There are no existing large-scale programs that can be examined for cost-effectiveness. Tentative projections, however, have been made of the cost-effectiveness of immunization strategies for China and Indonesia, where programs for HBV vaccination are under active consideration or in the early stages of implementation. In addition, the ITFH has made estimates for a prototypical program in a high-prevalence country.

Recast in annual percentage of per capita GNP, the costs for the three nonscreening programs lie within a range of 19 to 88 per undiscounted death prevented and 1 to 6 per undiscounted year of life gained (table 21-5). These costs, although greater than those for tobacco prevention programs, make HBV immunization an attractive candidate for inclusion in a cancer

Table 21-5. Cost-Effectiveness of Hepatitis B Vaccine in Various Settings

Setting	Percent GNPN per death prevented [a]		Percent GNPN per year of life gained [a]	
	$ra - 0$	$ra - 0.03$	$ra - 0$	$ra - 0.03$
Indonesia[b]				
Immunize all newborns	87	404	6	25
Screen mothers and vaccinate newborns at risk	151	700	9	44
China[c]				
Immunize all newborns	74	340	5	22
Screen mothers and immunize newborns at risk	77	356	5	23
Hypothetical example[d]				
Low-cost estimate	19	87	1	6
High-cost estimate	88	408	6	26

Notes: Effects include prevention of excess mortality from hepatitis B, liver cancer, and cirrhosis; it is not practical to identify liver cancer as the sole objective. The discounted values assume that intervention occurs at age 0 and the average HBV-caused death occurs at age fifty-two. The GNPN is estimated at 810 yuan.

a. Discount rate.

b. Widjaya (1988) calculated the cost per carrier prevented. This has been converted to deaths prevented and years of life gained using an excess mortality rate of 0.25 and sixteen years of life lost per HBV-associated death. Widjaya assumed vaccine cost of US$15 (does not include delivery cost). The program costs have been recalculated using vaccine cost of US$1.50 per dose and estimated delivery cost of US$1.20 per dose. Calculated for 1985, the GNPN is estimated to be 588,000 rupiah.

c. Circa 1986.

d. Assumes no screening. The ITFH 1988 estimates, which are given in U.S. dollars, have been converted to percent GNPN. Assumes per capita GNP of US$400.

Source: Widjaya 1988; Barnum 1988; ITFH 1988.

prevention strategy. Discounting affects the estimated cost-effectiveness of HBV programs more than many other interventions because of the long lag between delivery of the intervention (which occurs at birth) and prevented death (which, for liver cancer or cirrhosis occurs at an average age of about fifty-five years). Using a 3 percent discount rate, we find that the cost per death prevented ranges from 87 to 408 and the cost per YLG ranges from 6 to 26. Even after discounting, HBV vaccine remains an attractive program possibility.

The cost-effectiveness of a maternal screening program is equal to the newborn program in the China example but is much less cost-effective than the newborn program in the Indonesia example (table 21-5). In both examples, however, cost-effectiveness calculations include only the deaths directly prevented in the newborn cohort. Additional deaths will be prevented from reduced transmission of hepatitis to other cohorts in the future. This indirect effect will be substantial for the total immunization strategy but only modest for the screening strategy. Thus the total immunization strategy is superior, because it holds out the possibility of a dramatic containment of hepatitis B in the future, instead of continued endemicity that would result from the screening strategy.

FOOD AND ALCOHOL. Abundant epidemiological evidence links dietary habits to occurrence of cancer. There is still considerable uncertainty, however, both about the actual dietary constituents that influence risk and about the proportion of cancer occurrence that can be explained by diet. Alcohol consumption clearly increases risk of cancers of the oral cavity and esophagus. Alcohol has been implicated as a cause of breast cancer and large bowel cancer, although the epidemiological evidence is not conclusive. Consumption of foods contaminated with aflatoxin (produced by *Aspergillus flavus* fungal growth on stored peanuts and grains) is likely to be a cause of primary liver cancer. With the exception of these substances, however, no single component of diet has been conclusively shown either to cause or to prevent cancer (Doll and Peto 1981; Willett and MacMahon 1984; Byers 1988). Nevertheless a number of intriguing relationships between diet and cancer have emerged from epidemiological studies. These include positive associations between poorly preserved or pickled foods and stomach cancer, traditionally prepared salted fish and nasopharyngeal cancer (among southern Chinese), and total fats (or perhaps saturated fats) and large bowel cancer. Interesting negative (protective) associations have been observed between vegetable or fruit consumption (or their constituents such as beta-carotene and fiber) and a variety of epithelial cancers, most notably lung and colorectal cancer.

Estimates of the proportion of cancers attributable to diet in the industrial world range widely from about 10 percent to more than 70 percent. Given this uncertainty, and the lack of firm conclusions about most postulated dietary causes of cancer, it is not possible to predict the benefits (in reduced cancer) that may accrue from dietary interventions. An assessment of the costs and value of dietary interventions must await the results of further studies, which may likely include randomized controlled trials. Several relationships between diet and cancer, however, are particularly relevant in the developing world, and these may well figure in a natural cancer control program. Especially noteworthy are the relation between aflatoxin-contaminated food and liver cancer and between traditional Chinese salted fish and nasopharyngeal cancer. Other aspects

of diet that merit attention in the developing world include consumption of alcohol (related to esophageal and oral cancers), poorly preserved foods (related to stomach cancer), and obesity.

In countries with high rates of liver cancer, a program to reduce aflatoxin intake (by better storage of grains and peanuts and by monitoring the aflatoxin content of commercial foods) may be justifiable as an adjunct to hepatitis B virus immunization. At present, one cannot precisely estimate the amount of liver cancer that could be avoided through reduction of aflatoxin. Although hepatitis B immunization programs may eventually prove to be the most cost-effective method for preventing liver cancer, they will not benefit people who are already infected with HBV and thus at risk for developing liver cancer. Aflatoxin appears to be an important cofactor leading to liver cancer development in HBV carriers (Bulatao-Jayme and others 1982; Yeh and others 1989); thus reduction of aflatoxin consumption offers promise for reducing liver cancer mortality in the near future, whereas immunization programs are unlikely to show a substantial benefit for forty or more years. Consumption of traditionally prepared salted fish in southern China (and in areas settled by migrants from southern China, such as Singapore) is strongly related to nasopharyngeal cancer (Yu and others 1986). Educational programs to discourage the practice of feeding salted fish to infants, weanlings, and children may be justifiable in these populations. It also seems reasonable to discourage consumption of other traditionally prepared foods that are high in volatile nitrosamines in countries where nasopharyngeal cancer is common (Poirier and others 1987).

In certain countries the possibility of reducing cancer occurrence may provide additional justification for implementing programs to decrease alcohol consumption, although the primary value of these programs is to reduce injuries and other ills. The cancer prevention benefits of reduced alcohol consumption (historically, difficult to achieve through government policy) cannot be reliably assessed, however, because the proportion of oral and esophageal cancers caused by alcohol is uncertain. The contribution of tobacco use to these cancers appears to be greater than that of alcohol.

Many other foods and nutrients are strongly suspected of influencing cancer occurrence, and these have figured in national dietary policies in the industrial world. For example, Americans are advised to eat a diet containing less fat and more fiber and to consume larger amounts of fresh fruits and vegetables. There is no conclusive information from scientific studies that these recommendations will lower cancer risks. Nevertheless, several expert review groups have concluded that one or more of these recommendations should be presented to the public as prudent advice for dietary change.

The justification for advising people to eat more fruits and vegetables is that epidemiological studies have shown decreased risks for many types of cancer in people whose diet is high in these foods (National Research Council 1982). Also fruits and vegetables may displace other, less desirable, foods from the diet. The evidence linking lowered risk of cancer with consumption of fresh fruits and vegetables should be carefully considered in discussions of national food policy. At the minimum, it would be prudent to avoid strategies that discourage production and consumption of these foods.

Obesity itself, apart from constituents of diet, is also associated with cancer mortality (Lew and Garfinkel 1979; Simopoulos 1987). The association is particularly notable for female breast and endometrial cancers. Of course, obesity is a complex phenomenon, and its occurrence is determined by genetic factors and physical activity as well as by caloric intake. Still, obesity often appears to accompany other features of economic development, and it is associated with diabetes, cardiovascular diseases, and other conditions in addition to cancer. It therefore merits consideration for public health preventive programs.

Diet affects many diseases besides cancer, and it would be unwise to alter diet without considering all the potential health consequences. Also, dietary change has economic and social implications. Planning and application of dietary strategies to prevent cancer should therefore occur only within the context of an overall national policy on diet. The relative importance of nutritional deficiency diseases, obesity, cardiovascular disease, diabetes, cancer, and other diet-related conditions must be considered country by country. Likewise, the expected economic consequences, in changing agriculture and food marketing, must be considered if a successful dietary intervention is to be accomplished.

ENVIRONMENTAL AND OCCUPATIONAL PROGRAMS. Exposure to environmental and occupational factors accounts for an undetermined but probably small number of cancers in the developing world. In the industrial world the actual contribution of such factors to cancer occurrence has been the subject of considerable debate (Doll and Peto 1981). Much confusion has arisen about the definition of "environmental" causes of cancer. If "environmental factors" are taken to mean only agents in the ambient environment (excluding diet and habits such as smoking, chewing, and so on), then only a small proportion (probably less than 10 percent) of cancers can be attributed to these causes. Nevertheless, in certain highly exposed groups, usually defined by occupation, environmental agents are more important.

Several environmental agents have been identified as possible causes of lung cancer. These include both ambient and occupational exposure to industrial chemicals and radon. These causes are important in selected subpopulations in which exposure is intense. For example, workers involved in the manufacture of asbestos, chromates, and ion exchange resins (involving chloromethylethers) are all at elevated risk of lung cancer. Likewise, underground miners exposed to high levels of radon have an increased risk of lung cancer.

Cigarette smoking acts with environmental factors to increase greatly the risk of lung cancer. Before implementation of protective measures for asbestos workers in the United States, asbestos workers who smoked cigarettes had approximately five times the risk of lung cancer as smokers who did

not work with asbestos and more than fifty times the risk of people who neither smoked nor worked with asbestos. Similarly, the risk for uranium miners who smoke cigarettes is four times the risk of smokers who are not miners. Nonetheless, within the United States population as a whole, these other environmental factors are of little significance when compared with the effect of tobacco smoking. After taking account of the effects of other known causes of lung cancer, tobacco smoking still appears to account for at least 80 to 90 percent of lung cancer deaths in North America (Doll and Peto 1981).

Present information does not appear to warrant a general recommendation regarding environmental and occupational interventions to control cancer. For limited exposed populations these types of intervention may be cost-effective or necessary on moral grounds. Asbestos merits particular concern in this regard for two principal reasons. First, it is widely used in many developing countries in applications for which there are no cheap substitutes. Second, the rising prevalence of cigarette smoking greatly magnifies the potential for asbestos-related lung cancer. Programs to reduce workers' exposure and to use safer forms of asbestos will likely be worthwhile for many countries. For much of the developing world, however, control of environmental and occupational carcinogens appears to deserve a lower priority than other, proven cancer prevention activities.

CANCER PREVENTION BENEFITS AND OTHER HEALTH MEASURES. Programs directed toward other important diseases may, as an ancillary benefit, also help to control cancer. For example, schistosomiasis is clearly associated with urinary tract cancer (in the case of *Schistosomiasis hematobium*) and possibly related to bowel cancer (in the case of *S. japonicam* and *S. mansoni*). An evaluation of the cost-effectiveness of a mass treatment program to control *S. hematobium*, for example, should take account of the expected reduction in urinary cancers that would result. Likewise, control of *Clonorchis* and *Opisthorchis* infection, besides reducing acute morbidity, will lessen the risk of biliary tract cancer. Last, programs to decrease spread of sexually transmitted diseases seem likely to diminish cervical cancer occurrence. In all these examples the reduction of cancer occurrence would be a secondary benefit that would be realized only years (or decades) after an effective program was implemented.

Secondary Prevention

The cost-effectiveness of secondary prevention (that is, screening and early detection) programs is dependent on the incidence of the disease in question, the technical feasibility of screening and treatment at early stages in the cancer's development, the possibility of targeting to reduce costs by covering groups at highest risk, and the availability and cost of appropriate health infrastructure so that the screening can be carried out with accuracy and the findings followed with an effective intervention. Among the ten primary cancers, on the basis of the experience in industrial countries, cervix and breast cancer hold greatest promise as candidates for national-level screening programs. These are discussed in detail later.

Large bowel cancer and oral cancer are also of interest, although evidence supporting the value of screening for these two tumors is inconclusive. Several procedures for colorectal cancer screening have been proposed, but none has yet been shown clearly to reduce the risk of death from this condition (Chamberlain and others 1986; Clayman 1989; Fleischer and others 1989; Knight, Fielding, and Battista 1989). Institution of screening programs cannot now be recommended as a public policy, but further tests of screening efficacy and controlled clinical trials are clearly worth undertaking. Examination by flexible sigmoidoscopy appears particularly promising as a procedure, although not in countries with limited health resources. Screening for oral cancer in conjunction with other medical procedures, such as dental care or general care, theoretically should prevent deaths from this disease. The expected low cost of screening (by simple inspection), and the possibility of identifying premalignant changes (leukoplakia), make oral cancer a good prospect for intervention (McMichael 1984). Also, high-risk individuals (those who chew or smoke tobacco) are readily identifiable. There have not, however, been any published studies showing the effectiveness of oral cancer screening. In countries, such as India, with high mortality rates for oral cancer, screening programs may now be worth undertaking but only within a research context.

Most other cancers such as lung, liver, esophageal, and stomach cancer are not suitable targets for a screening program in a developing country.[6] Although they can be detected in a presymptomatic phase, no controlled studies have shown that screening reduces the risk of death from these tumors. Also, these tumors tend to progress rapidly to a clinically symptomatic phase, so there is only a brief period during which the cancer is screen detectable but not symptomatic.

CERVICAL CANCER SCREENING (PAP SMEAR). Because of its high incidence in many lower-income countries, screening for cervical cancer is among the most promising of the secondary prevention possibilities. The objective of cervical cancer screening is to detect neoplastic cells at an early stage when a relatively low-cost and low-risk surgical procedure can be used to remove the cells and prevent occurrence or spread of invasive cancer. The cost-effectiveness of cervical cancer screening has been debated in the literature, but evidence in support of screening has become compelling (Cramer 1982; Lynge, Madsen, and Engholm 1989), and cervical cancer screening is an important component in the World Health Organization's strategy for combating cancer (WHO 1988b). The cost-effectiveness of screening, however, varies greatly with the setting in which a program is carried out. Important factors determining the advisability of the test include incidence and mortality rates (and therefore the prevalence of occult disease), type of program (mass screening or integrated medical examination), availability of adequate facilities for following the test findings, accuracy of laboratory facilities, and cost of the test and follow-up procedures.

The World Health Organization (1986b) has recommended that in low-income countries every woman should be screened once in her lifetime between the ages of thirty-five and forty years. If additional resources are available, screening should take place at intervals of ten years for women between the ages of thirty-five and fifty-five. In middle-income countries the interval should be increased to five years. The cost-effectiveness of tests falls off rapidly as the frequency of testing goes much above three to five years and as the age of testing falls below thirty-five.

Estimates of the cost-effectiveness of cervical cancer screening, in percentage of per capita GNP per year of life gained, range from about 70 to 300 percent per undiscounted death prevented, or 4 to 18 percent per year of life gained (table 21-6). Because of the brief time between the start of screening and the average age of death, the effect of discounting is not great. Using a discount rate of 3 percent, we find that the cost per year of life gained ranges from 5 to 26 percent GNPN. At the upper extreme, cervical cancer screening is not competitive with other health interventions, whereas at the lower extreme the program would be an attractive component of a chronic disease strategy. Clarification of the epidemiological basis and cost-effectiveness of program design should be made in individual countries before embarking on a program of secondary cervical cancer prevention. Cost-effectiveness will be greater in countries with higher rates of cervical cancer and in those with clearly identifiable high-risk groups. It will be lower where cultural norms prevent women from having pelvic examinations and where the quality of cytology laboratory work is low.

BREAST CANCER SCREENING. Breast cancer screening can be carried out through a physical examination by a health care worker (Baines, Miller, and Bassett 1989) or a combination of a physical examination and mammography. Controlled clinical studies with long-term follow-up have demonstrated that a physical examination combined with mammography can reduce breast cancer mortality by about 20 to 30 percent (Shapiro and others 1982; Tabar and others 1985; Day and others 1986). Breast self-examination has also been promoted as a secondary prevention policy, but evidence for its effectiveness in reducing mortality is weak (Day and others 1986).

The cost-effectiveness of breast examination using mammography is much less than that of cervical cancer screening in the examples we considered. The estimated cost per YLG from mammography ranges from about 100 to 200 percent GNPN using a discount rate of 3 percent. The estimated cost per YLG from the physical examination alone is, however, competitive with other prevention activities. Using only a physical examination and discounting costs and effects at 3 percent, the cost per YLG was 12 percent GNPN as recalculated from the results reported in a study by D. Eddy (1981; see table 21-7).

Treatment

The three primary modalities for treating cancer are surgery, radiation therapy, and chemotherapy (including hormonal manipulation). Surgery alone offers a chance of cure for cancers of the breast, uterine cervix, colorectum, and oral cavity. Although some cancers of the stomach, lung, liver, and esophagus are also curable by surgery, their number is very small. The surgical treatment required for early stage cancers of the breast, cervix, colorectum, and oral cavity does not require highly technological facilities, nor does it require training beyond that ordinarily received by surgical specialists. The procedures generally take approximately two to four hours to complete and are associated with a hospital stay of seven to fourteen days. Accurate assessment of the degree of cancer spread (staging) is important so that performing surgery is avoided on patients in whom the procedure cannot be curative, and it necessitates reliable diagnostic imaging facilities.

Table 21-6. Cost-Effectiveness of Screening for Cervical Cancer

Study	*Percent GNPN per death prevented* [a]		*Percent GNPN per year of life gained* [a]	
	ra – 0	*ra – 0.03*	*ra – 0*	*ra – 0.03*
Parkin and Moss (United Kingdom) [b]				
Five-year interval, age 35–64	66	94	4	5
Five-year interval, age 25–64	154	220	7	11
Barnum (China) [c]				
Five-year interval, age 35–59	310	390	18	26
Luce (United States) [d]				
Five-year interval, age 30–39	138	250	13	25
Three-year interval, age 30–39	145	290	12	23

a. Discount rate.

b. Based on model identified as "H3C" in Parkin and Moss 1986. Their results are scaled in terms of unit costs representing the cost for a routine screening. To convert their results to percent GNPN, 1 unit of input was evaluated as 4.6£ (1982 prices), using a price index for medical services in the United Kingdom, and then rescaled using a 1982 GNPN of 4,907£. Discounting assumes an average of twelve years from the age of screening to the averted cancer mortality.

c. Estimates are not based on as complete a model as other two studies. For example, false positives and false negatives are not included.

d. Luce results reported in terms of 1979 U.S. dollars per death prevented and year of life gained from using a 10 percent discount rate. These have been converted by interpolating from Luce's discount rate sensitivity table and using a 1979 GNPN of US$10,810. Luce's "Low cost" public provider model has been used.

Source: Luce 1980; Parkin and Moss 1986; Barnum 1988.

Table 21-7. Cost-Effectiveness of Screening for Breast Cancer

Study	Percent GNPN per death prevented [a]		Percent GNPN per year of life gained [a]	
	ra – 0	*ra – 0.03*	*ra – 0*	*ra – 0.03*
Eddy[b]				
Physical exam only	—	—	—	12
Physical exam and mammography, one-year interval, age 50 and older[c]	—	—	—	97–210
Schwartz, three-year interval, age 40–70[d]	—	—	15	135

— Data not available.

a. Discount rate.

b. Assumes U.S. GNPN of $12,800.

c. The costs and effects are incremental with the addition of mammography to a routine annual physical examination. Based on U.S. GNPN of $10,600 (1979). Based on present value of total incremental cost ranging from $482 to $1,042.

Based on the increase in life expectancy from age forty. Assumes a cost of US$100 per screening and eleven screenings between age forty and seventy. Based on U.S. GNPN of $10,600 (1979).

Source: Schwartz 1978; Eddy 1981.

Radiation therapy involves administration of high-energy radiation in an effort to kill tumor cells. The technique requires sophisticated equipment and skilled therapists, who are likely to be found only in technologically advanced tertiary care centers. Radiation therapy is capable of curing lymphoma (particularly Hodgkin's lymphoma) and cancer of the cervix. Radiation therapy is useful for control of breast cancer and lung cancer, although it only rarely cures lung cancer. Most courses of radiation therapy must be administered over a prolonged period (usually several weeks), but the patient may not have to be kept in the hospital.

Chemotherapy is administration of drugs that kill cells or inhibit their growth. Chemotherapy is potentially curative in leukemia and certain lymphomas. It also contributes to length of survival and possibility of cure in breast cancer. Chemotherapy provides palliation in certain forms of lung cancer. Intensive chemotherapy such as that given for most lymphomas and leukemias requires highly trained physicians who have substantial experience with administration of these toxic agents. Less toxic chemotherapy for relief of symptoms often can be carried out in primary medical settings, providing that consultant guidance is readily available. Many of the drugs used for chemotherapy are expensive, and they require close monitoring of laboratory tests and intense skilled nursing support because of side effects. An exception is the antiestrogen drug Tamoxifen. It clearly reduces risk of recurrence and death in breast cancer yet is relatively free of toxic side effects, is simple to administer in oral form, and should be available at low cost in most countries (WHO 1985).

More recent advances in cancer treatment have shown the importance of multidisciplinary management, involving more than one treatment modality. This strategy requires the combined efforts of highly trained professionals and is possible only in the context of a technologically sophisticated tertiary care center. Many of the gains noted in the probability of survival of patients with certain cancers (particularly leukemias and lymphomas) are attributable to use of multimodal therapy.

Application of the most advanced therapy can be vastly expensive. For some cancers, for example, childhood lymphocytic leukemia, treatment may continue for a prolonged period and require repeated hospitalization, intensive chemotherapy, and radiation therapy. During the course of treatment the child may require sixty to ninety days in the hospital.

A policy decision to provide access to this type of technologically advanced treatment has implications beyond the immediate cost of the procedure. First, a facility must be developed that has the technological capacity to support advanced therapies. This involves diagnostic imaging capabilities, advanced laboratory facilities, and radiation therapy devices. Second, highly trained and experienced personnel are needed from both the medical and nursing professions to carry out the therapy. Third, the patients who are likely to benefit from advanced multimodal therapy are relatively few in number, so referral to a few specialized treatment facilities will be necessary. To provide ready access to advanced cancer treatment will require the development of a system of central treatment facilities with an outlying referral network. This implies a heavy investment in facilities located in urban areas and will further concentrate resources away from rural populations.

Cost-Effectiveness of Treatment

Given the resource intensity of cancer treatment, evaluation of its cost-effectiveness is particularly important to make informed planning decisions. Cancers differ greatly in severity and potential for treatment or prevention, and, for the most part, it is necessary to consider the effects and costs for separate types of cancer. In the remainder of this section we provide a cost-effective analysis of cancer treatment using United States data to model effectiveness and general information to model costs in a prototypical country. The results are acknowledged to be highly approximate, and our intention is to allow rough comparisons of the cost-effectiveness of treatment and prevention. For certain cancers, notably cervix and breast, and perhaps colorectal and oral cancer, the close link between secondary prevention and treatment prevents a clear assignment of gains in survival to treatment per se. For these cancers

screening and treatment need to be considered as joint interventions if the full cost-effectiveness of treatment is to be achieved. In fact, the cost-effectiveness of treatment of cancers for which screening is feasible exceeds the estimates in this section (which are based on an average for all stages), because the effect of treatment on early stage cancer is greater and, in some instances, the cost of treatment is less.

EFFECTS. We approximate the effectiveness of treatment using data on the change in survival rates for cancer in the United States from the period 1945–50 through the years 1955–60 to 1975–80. Conceptually, the objective is to estimate the benefits in developing countries of treatment in a higher-level hospital with relatively modern technology in comparison with treatment at an entry-level hospital or with no treatment or only palliative care. As an approximation, the higher-level hospital is equated with the level of care in the United States in the period 1975–80, and the low-level care alternative is equated with the level of treatment in the United States during 1945–50. Baseline, minimal treatment survival rates are specified arbitrarily after a literature search of technical improvements in cancer prior to 1940.

Equating institutional care at various levels with chronological change in cancer care in the United States is obviously only an oversimplification because, on the one hand, there are a few modern techniques that can be delivered with effect and at low cost at smaller, low-level institutions and, on the other hand, there were some effective treatments used in large, technically advanced hospitals in the United States in the years 1945–50. During the last forty years, however, there have been substantial advances in radiation, chemotherapy, and surgery. Radiation therapy has advanced through development of new sources of radiation and techniques that allow better control of the intensity and the focus of radiation. Chemotherapy has advanced with the development of new drugs and their use in combined therapies. Surgery has improved in safety and precision. Another change during the thirty-year period has been in the accuracy of diagnostics, which has made it possible to identify cancers at an earlier stage.

All these factors are likely contributors to the changes that can be seen in relative survival in table 21-8.[7] It would be a mistake to view the apparent improvements in survival as entirely attributable to improved therapy. Part of the recorded increase may also be due both to earlier diagnosis and to detection of less aggressive tumors, factors which give an illusion of improved survival without any true change in the underlying risk of death. The size of these effects is debated in the literature and unknown, but in any case, the apparent increase in survival almost certainly overestimates the effect of new therapy techniques.

The data show very little improvement in survival for esophageal, stomach, and liver cancer. Lung cancer improvements that are shown are small and difficult to attribute to technical improvements. Although there have been modest gains in treating small cell carcinoma, this cell type represents less than 20 percent of all lung cancer. Much of the increase that is shown is likely an artifact resulting from earlier diagnosis. Improved survival for leukemia (and perhaps for breast cancer) is more reflective of the effects of new therapies. In the analysis below we lack the quantitative information to make an adjustment for the effects of earlier diagnosis and different spectra of tumor aggressiveness, but these sources of error should be borne in mind when one interprets the results.

The effectiveness of treatment is estimated by calculating the implied gain in years of life in going from the baseline fatality rates that would exist with only minimal treatment to the fatality rates after treatment equivalent to the United States level in the period 1975–80. The fatality rates implied by the published survival data and the baseline fatality rate used in the analysis are summarized in table 21-9.

COSTS. Surprisingly few studies have been done on the total direct costs incurred over the course of specific cancers. Costing cancer is particularly difficult because for given cancers there may be a number of treatment options at each stage of the disease, and the duration of treatment may last several years. Also, treatment procedures and therefore the costs of treatment vary considerably for the different types of cancer.

Table 21-8. Five-Year Relative Survival for Cancer in the United States, by Year

Site or type of cancer	*1950*	*1960*	*1970*	*1980*
Mouth/pharynx	0.45	0.45	0.43	0.53
Esophagus	0.04	0.04	0.04	0.06
Stomach	0.12	0.11	0.13	0.16
Colon/rectum	0.41	0.44	0.46	0.53
Liver	0.01	0.02	0.03	0.03
Lung	0.06	0.08	0.10	0.13
Breast	0.60	0.63	0.68	0.75
Cervix	0.59	0.58	0.64	0.67
Leukemia	0.10	0.14	0.22	0.33

Source: Axtell, Asire, and Myers 1976; American Cancer Society 1987.

Table 21-9. Estimated Five-Year Fatality for Cancer, by Year

Site or type of cancer	*Baseline minimal treatment*[a]	*1950*	*1960*	*1970*	*1980*
Mouth/pharynx	0.82	0.58	0.58	0.60	0.50
Esophagus	0.97	0.97	0.97	0.97	0.95
Stomach	0.90	0.90	0.91	0.89	0.86
Colon/rectum	0.75	0.64	0.61	0.59	0.52
Liver	0.99	0.99	0.98	0.97	0.97
Lung	0.95	0.95	0.93	0.91	0.89
Breast	0.75	0.47	0.43	0.38	0.31
Cervix	0.80	0.50	0.50	0.45	0.41
Leukemia	0.90	0.90	0.86	0.78	0.67

Note: Five-year fatality computed as $F = 1 - R * S$, where R is the relative survival given in table 21-8 and S is overall survival (for all stages) from United States life tables for 1950–80.

a. Either 1950 fatality or higher rate implied from literature search.

Source: Axtell, Asire, and Myers 1976; American Cancer Society 1987.

For the purposes of this study, we approximated the costs of treatment using information on the relative costs of treatment for different cancers in the United States (Cromwell and Gertman 1979; Rice, Hodgson, and Kopstein 1985). These costs were then scaled to the cost of tertiary treatment and expressed as a percentage of per capita GNP for a lower-middle-income developing country. Although this procedure is inexact, it is probably sufficient for the comparisons between cancers and between prevention and treatment that are sought here. In table 21-10 we present the estimates of total costs per case, varying from a low of about 175 percent GNPN for cervical cancer to 780 percent GNPN for lung cancer.

COST-EFFECTIVENESS. The costs and effects derived in the two preceding sections can be compared to give the costs per year of life gained from treatment. Looking first at the cost per YLG for the average of cancer in all stages (table 21-11), we find that the results suggest that it is relatively cost-ineffective to treat esophageal, stomach, liver, and lung cancer and more cost-effective to treat colorectal, cervical, and breast cancer. To compare extremes, the cost per year of life gained from treatment for esophageal cancer is more than 100 times that for cancers of the breast, mouth, and cervix. The results also suggest that it is much more cost-effective to treat cancers at younger ages; in particular, the cost per year of life gained for treatments at age fifty and over are very high.

The analysis above underestimates the true costs and overestimates the effects and therefore must be interpreted cautiously. First, only the direct costs of health services are included. Costs to patients and their families in travel to the hospital and provision of supplementary care or food are not included. Second, for several cancers, especially of a certain type and in advanced stages, the number of years of additional life is very small and may be largely an artifact of earlier detection, diagnosis of less malignant tumors, and staging changes (Feinstein, Sosin, and Wells 1985). Third, there is no adjustment for quality of life. This omission can be especially important for the marginal gains (in extended life) for treatment of later stage cancer and for treatment of esophageal, stomach, lung, or other cancers for which the gain in fractional years of life follows debilitating treatments that usually result in only short periods of remission.

The analysis is also based on improvements in survival rates in the United States, where there has been an increased emphasis on early detection during the last forty years and where there is substantial training and treatment capacity. This link between detection and treatment is especially important as an underlying factor in the cost-effectiveness of treatment for cancers of the mouth, cervix, breast, and colon. It is important to emphasize the link between detection and treatment because it is not useful to develop treatment capacity in the absence of improved detection; nor is it useful to develop detection programs in the absence of treatment capacity. This link has been underlined by the World Health Organization, which stresses the importance of linking the development of therapy with early referral (WHO uses the term "down staging") and improved training for cancer detection among primary health care workers (Stjernsward 1990).

PAIN RELIEF. An important component of palliative care for cancer patients is adequate treatment of pain (Portenoy 1988). More than 80 percent of cancer is not detected until an advanced stage at which treatment other than palliation is not effective (Stjernsward 1988). A WHO document setting out guidelines on cancer pain relief estimates that 50 to 70 percent of cancer patients experience pain (WHO 1986a). Of these, pain is moderate to severe in about 50 percent and very severe in 30 percent. The World Health Organization recommends a three-stage analgesic program going from nonopioids (such as aspirin or paracetamol) for mild pain, through weak opioids (such as codeine plus paracetamol) for moderate pain, to strong opioids (morphine) for intense pain. They note that these agents, possibly supplemented by adjuvant drugs (see the details in WHO 1986a and Stjernsward 1988), can provide relief in 90 percent of cancer patients with pain.

Past inadequacy of cancer pain control is attributable to a lack of recognition by health care professionals that effective methods existed for cancer pain management, a lack of availability of the required drugs, unreasonable fears concerning addiction, and poor education of health professionals on can-

Table 21-10. Cost per Case Treated
(percent GNPN)

Site or type of cancer	Costs relative to average for US [a]	Costs per case in high-income country [b]	Cost per case in lower-middle-income country [c]
Mouth/pharynx	0.76	79	243
Esophagus	1.11	115	709
Stomach	1.07	112	687
Colon/rectum	1.05	110	336
Liver	1.13	118	727
Lung	1.22	127	782
Breast	0.65	67	206
Cervix	0.54	57	174
Leukemia	1.09	114	700
Average	1.00	104	641

a. Based on 1969–71 average direct costs for cancer treatments as reported in Cromwell and Gertman 1979.

b. The number of bed-day equivalents for the cost of the average cancer in the United States was multiplied by the cost of a bed-day (expressed as percent GNPN) to obtain the cost of an average case of cancer. This average was, in turn, multiplied by the relative costs in the first column to obtain the costs for individual cancers. In 1980 the average direct cost of cancer in the United States was fifty-three times the cost of the average bed-day based on a reanalysis of data in Rice, Hodgson, and Kopstein 1985 and thirty-seven times based on 1969–71 data in Cromwell and Gertman 1979; 40 is used for these calculations. The percentage GNPN per bed-day in a large urban hospital remains relatively stable over a sample of countries, 2.6 was used for these calculations.

c. Because the technical hospital procedures involved in cancer therapy can have a high foreign exchange content when cost is determined by international prices, the estimated cost is a weighted sum of a foreign exchange component (including specialized training, equipment, and pharmaceuticals) and a local component. The calculations are made for a lower-middle-income country with a per capita GNP of US$1,500. As an approximation, it is assumed that the foreign exchange content is 0.2 for early stages of oral, cervical, breast, and rectal cancer treatment and 0.5 for all other cancers.

Source: Cromwell and Gertman 1979; Rice, Hodgson, and Kopstein 1985.

Table 21-11. Cost per YLG Gained from Tertiary-Level Treatment in a Lower-Middle-Income Country, by Age at Diagnosis
(percent GNPN)

Site	Average age	65 years	60 years	55 years	50 years	45 years	40 years
Undiscounted							
Mouth/pharynx	44	179	80	51	38	30	25
Esophagus	3,574	8,755	3,891	2,502	1,843	1,459	1,208
Stomach	2,462	6,525	2,900	1,864	1,374	1,087	900
Colon/rectum	126	472	210	135	99	79	65
Liver	3,315	13,011	5,783	3,717	2,739	2,168	1,795
Lung	1,183	3,075	1,367	879	647	512	424
Breast	26	93	46	31	23	19	16
Cervix	27	69	35	23	17	14	12
Discounted at 3 percent							
Mouth/pharynx	55	187	89	62	49	41	36
Esophagus	4,056	9,147	4,367	3,010	2,374	2,008	1,772
Stomach	2,826	6,817	3,254	2,243	1,769	1,496	1,320
Colon/rectum	154	493	235	162	128	108	96
Liver	4,083	13,593	6,489	4,473	3,528	2,984	2,633
Lung	1,354	3,213	1,534	1,057	834	705	622
Breast	33	122	58	40	32	27	24
Cervix	32	90	43	30	23	20	18

Note: Costs are averaged over all stages. Costs per YLG gained from tertiary level treatment of leukemia diagnosed in a ten-year-old are 48 percent of GNP undiscounted and 100 percent discounted at 3 percent.
Source: Authors.

cer pain management. Legislative reform, better pharmaceutical management, and improved training can remove these blocks to better pain therapy.

Adequate treatment of pain could alleviate much suffering while placing fewer demands on medical resources than ineffective attempts at higher-level curative treatment. For example, for an average duration of pain therapy of ninety days, the cost of drugs and outpatient delivery in a lower-middle-income developing country would be about $18 to $65 per case, or 1 to 4 percent GNPN, for, respectively, mild to severe pain management.[8] This would represent less than 1 percent of the cost of inpatient tertiary treatment of, say, lung or esophageal cancer.

COST-EFFECTIVE TREATMENT POLICY. The results of the cost-effectiveness analysis can be helpful in fashioning a policy to increase dramatically the effective use of secondary and tertiary hospital resources in place of available space to treat all cancer on the basis of random referral or first come, first serve. Applying a criteria of no more than 50 percent GNPN per year of life saved and bearing in mind the cautionary comments noted in the preceding paragraph, a possible policy would be the following:

- Use existing referral capacity to treat younger patients with early stage cancers amenable to curative treatment, especially breast, mouth, cervical, and possibly colorectal cancer.
- Use existing tertiary-level referral capacity to treat children with leukemia and lymphoma.
- Provide for decentralized supportive care and symptom relief for the vast majority of other cancer patients using community-based alternatives for palliative care. For patients with breast cancer, Tamoxifen therapy could also be accomplished at this level.

Such alternatives include community-staffed nursing homes, health center outpatient care and hospices for the terminally ill, and home beds managed from lower-level hospitals. Almost all patients with stomach, liver, and lung cancer would receive care at this level. Older patients and those with advanced disease would not be referred for curative therapy, but reasonable efforts would be made to alleviate pain and suffering through use of palliative medications.

Developing a Strategy for Cancer

The World Health Organization has recommended the development of national cancer strategies based on surveillance and prevention programs tailored to local needs (Stjernsward and others 1985; WHO 1988b). The recommendations of WHO for the development of a national cancer strategy are especially important in countries in which infectious diseases have been reduced and life expectancies are lengthening. It is not effective to allow the resources devoted to combating cancer to be allocated without plan on an ad hoc basis depending on local interests. Instead, a national cancer strategy needs to be developed formally. Such a strategy would recognize local variations in cancer occurrence and risk factor prevalence. It would also allow setting an overall national strategy to combat cancer and

Table 21-12. Subjective Potential for Primary Preventive Activities for Cancer

Activity	Potential reduction of YLL	Feasibility[a]	Potential technical effect[b]	Persons covered per unit cost	Priority
Antismoking measures	High	Medium	High	High	Highest
Hepatitis immunization	Medium	High	High	Medium	High
Control of carcinogens in food[c]	Low	Medium	Medium	High	Medium
Reduced fat and increased fiber in diet	Unknown	Low	Unknown	High	Low
Occupational hazards					
Agriculture: pesticides, fertilizers, equipment	Low	Medium	High	Low	Low
Mining (dust exposure)	Low	High	Medium	Medium	Medium
Industrial safety	Low	High	High	Medium	Medium
Air pollution control	Low	Low	Low	Low	Low
Home environment: heating	Medium	Low	Medium	Low	Medium
Genetic screening and counseling	Low	Low	Medium	Low	Low

a. As demonstrated, for example, from implementation in other countries.
b. Related to prevalence of diseases affected, age and social characteristics of people affected, and effectiveness of program. A possible measure of effectiveness is healthy days of life saved.
c. Including aflatoxin.
Source: Authors.

mobilization of national resources to reduce cancer morbidity and mortality. This can be accomplished by setting priorities based on epidemiological information, demonstrating the value of specific cancer control activities, and anticipating changes in cancer incidence and resource needs. Several countries have developed national cancer control strategies on the basis of WHO recommendations. (Examples are Chile [WHO 1988a]; Indonesia [WHO/Indonesia, Ministry of Health 1989]; India [India, Ministry of Health and Family Welfare 1984; Nair 1988; and Bhargava, n.d.]; and Sri Lanka [Warnakulasuriya and others 1984].)

The cost-effectiveness analysis in the preceding sections is suggestive of appropriate priorities and does not take the place of the analysis of country-specific situations. The analysis does, however, provide an indication of the main components of a general cancer strategy. This section recommends a four-component general strategy for cancer consisting of primary prevention, secondary prevention, case management, and surveillance. The strategy is in direct contrast to the current picture in Europe and the United States in that it places less emphasis on centralized higher-level technology and acute care and greater emphasis on diffused basic institutional care and prevention. The strategy is based on the superior cost-effectiveness of prevention and lower-level case management.

Primary Prevention

Primary prevention programs are the key element in a strategy for cancer. Cancers targeted by the strategy and the program design need to be consistent with the pattern of cancers and risk factors in individual countries. The analysis above suggests that antismoking programs are of utmost priority and ought to be implemented as soon as possible. An antismoking campaign would be the single most cost-effective preventive activity and would likely be at least several times less costly per year of life saved than any other anticancer program. Smoking prevention and cessation programs could reduce lung and other cancers as well as provide benefits in reduced mortality from cardiovascular and nonmalignant respiratory diseases. Programs to reduce tobacco chewing are needed in countries in which oral cancer is prevalent. Hepatitis immunization is also likely to be cost-effective and should be a part of national strategies in countries in which HBV incidence is high, perhaps in conjunction with efforts to reduce aflatoxin exposure. These findings are consistent with a subjective evaluation of alternative primary prevention possibilities in the context of the limited resources of developing countries. A list of potential primary prevention activities is given in table 21-12. The activities are rated as to the importance of the associated disease as a cause of years of life lost, feasibility (including ease of behavioral modification), potential technical effectiveness, and cost per person covered.

Secondary Prevention

Analysis of the cost-effectiveness of individual secondary prevention programs is needed in specific country situations before they can be adopted as components of a national cancer strategy. Of all secondary prevention possibilities, cervical cancer screening through periodic pelvic examinations and Pap tests shows the most potential as a universal strategy component. In table 21-13 we list secondary prevention activities and give an evaluation of their potential as components of a national strategy. Again, as with the primary prevention activities, the list is subjective and only meant to be used as a basis for discussion. A salient aspect of the table, confirmed in several studies of specific secondary prevention activities, is the high cost of vertical secondary prevention programs in relation to benefits.

The high cost is a result of the fact that often thousands of people must be screened to identify one case of the disease and that most people who test positive in a screening program are found (on definitive testing) not to have cancer. Thus, the cost of screening per new case can be very high. Generally, secondary prevention is more attractive if the screening and early treatment costs are low, early therapy is effective, and the cost of late treatment is high (Kristein, Arnold, and Wynder 1977).

Secondary prevention generally appears less cost-effective than smoking prevention and HBV immunization. Still, well-planned and executed programs of cervical and (perhaps) breast cancer screening (using physical examination without mammography) directed at high-risk women may be cost-effective in areas of high incidence. Other screening programs are either of unproven benefit or do not seem highly cost-effective in most situations. But as the health sector develops and evidence of effectiveness accumulates, additional screening strategies may become cost-effective. Especially strong candidate programs for future evaluation are screening for oral and large bowel cancer.

Studies in the United States and Canada indicate that many secondary prevention programs are not cost-effective individually but may be important components of an integrated program. For example, pelvic examinations carried out as a result of mass vertical campaigns have been shown to be expensive per year of additional life gained among U.S. women, but when carried out as an integrated part of other activities, such as a periodic check-up or for contraceptive visits, the cost-effectiveness increases. Targeting also increases the cost-effectiveness of secondary prevention activities.

Case Management

Given the inadequacy of existing and projected resources to cope with chronic disease through conventional tertiary-level care, alternative modes of case management must be developed. Expansion of treatment care to cope with all cancer at the secondary or tertiary level would far exceed projected resources during the next twenty years in developing countries, and in any case it is not advisable, given the practicality of lower-level case management. Criteria need to be defined for developing and using upper-level and specialized facilities. To facilitate development of treatment policies, an evaluation of the effectiveness of treatment in extending the life of cancer patients must be made on a disease-by-disease basis and with differentiation by stage of disease and other prognostic factors.

Limited centralized facilities for treatment of selected referred cancer patients may be appropriate as discussed in the section on treatment, above, especially if improved treatment capacity is coordinated with earlier referral and diagnosis. Criteria for referral to treatment in higher levels of the health care system would make it possible to achieve longer and higher-quality lives for more people with existing and projected levels of resources. For most cancers, however, treatment with higher-level tertiary care is not cost-effective, and the investment by low-income countries in the special capacity for cancer treatment is not warranted. The small gains in life expectancy that may be achieved are often associated with a poor quality of existence, great discomfort, and stress. Use of scarce technical medical resources to treat cancer reduces their availability for other diseases for which there is greater probability of a favorable outcome from treatment and a higher quality of the years of life saved. Instead, development of less centralized, lower-level, treatment or case management alternatives, including adequate pain relief, would not only save resources but would also allow more humane care for the terminally ill.

Alternative lower-level and community-based care that could be developed includes substitution of outpatient for inpatient care; use of nonphysician professionals; use of home beds, community nursing care, and hospices; and an emphasis on palliative care rather than cure. Such care is not only of lower cost but may also be more humane.

Surveillance and Research

Rational planning of health resource allocation requires a continuous flow of information on disease occurrence, prevalence of etiological factors, and the cost and effectiveness of health interventions. This information can be used to set health investment priorities, to develop guidelines or triage rules for the use of health services, and to examine the cost-effectiveness of health activities from broad aspects of program strategy down to the assessment of specific technologies.

Ongoing data collection and research programs in most developing countries do not provide a good basis for building the capacity to analyze health program effectiveness in the future. These programs need to be strengthened and use made

Table 21-13. Subjective Potential for Secondary Preventive Activities for Cancer

Activity	*Potential reduction of YLL*	*Feasibility*[a]	*Potential technical effect*	*Persons covered per unit cost*	*Priority*
Pelvic exam	Medium	High	Medium	Low	Medium
Rectum, colon, prostate exam	Medium	High	Unknown	Medium	Low
Breast exam (mammography)	Low	Medium	Medium	Low	Low
Lung, stomach, esophagus cytology	High	Medium	Low	Low	Low
Oral exam	Medium	High	Unknown	Medium	Medium

a. As demonstrated, for example, from implementation in other countries.
Source: Authors.

of the analytical findings in cancer planning. For example, in China the Disease Surveillance Points System is providing crucial mortality information for setting health priorities on a disease-specific basis. This information, supplemented with cost data, will make it possible to analyze the cost-effectiveness of specific preventive and curative care interventions. It will also help to improve program efficiency by formulating criteria for prevention programs and triage rules for the use of curative care.

In-country capacity for research on questions of operational prevention programs needs to be developed. Particularly important are questions on the cost-effectiveness of health care technology. Cancer treatments and diagnostic procedures, perhaps more than those for other diseases, have led to adoption of high-cost technology with little established effectiveness. The contrast between the benefits of prevention and cure is acute for cancer. This contrast needs to be effectively and continually questioned using local analytical capacity.

Prototypical models for longitudinal operational research programs to reduce mortality and morbidity related to cancer and other chronic diseases need to be developed. Such programs would encompass a surveillance system for chronic diseases, an experimental framework for testing community-based interventions, and collaboration with the existing disease prevention and health care system in testing new programs. Activities that might come under examination include alternative antismoking measures, early detection of breast and cervical cancer, and a program of case management that employs home care and attempts to coordinate the capacity of different levels of care to provide cost-effective palliation. Establishment of such models in several regions with diverse epidemiological and socioeconomic environments would make it possible to test alternative primary and secondary prevention programs in specific local conditions.

Appendix 21A: The Ten Most Important Cancers in the Developing World

We consider each of the cancers individually, including a brief description of its biological characteristics, pattern of occurrence, important risk factors, effectiveness of treatment, possibility for screening, and potential for primary prevention. The descriptions, of necessity, are brief. Our purpose is to provide a background to the discussion in the text. More complete information can be obtained from any of several references, although Schottenfeld and Fraumeni 1982 is particularly recommended. Tables 21A-1 and 21A-2 provide rates and percentages of cancer incidence, respectively.

Stomach Cancer

Stomach cancer arises within the glandular cells that line the inside of the stomach. Almost all these tumors are adenocarcinomas. They may show varying degrees of differentiation and may take several forms; a polyp projecting into the lumen of the stomach, a superficially spreading mass on the stomach mucosa, or an infiltrating process in the stomach wall. In its early stages stomach cancer usually causes no symptoms. With more advanced disease patients experience lack of appetite, weight loss, abdominal pain, and other nonspecific digestive symptoms. Diagnosis is usually made by barium x-ray studies or gastroscopy. Within the United States more than 85 percent of patients have advanced disease at the time of diagnosis, and only 10 to 15 percent survive five years.

OCCURRENCE. About 670,000 cases of stomach cancer occur in the world each year, the cases being about equally divided between the industrial and developing countries. Mortality rates are particularly high (above 30 per 100,000 for males) in Japan, Chile, Hungary, and Poland. They are much lower in United States whites (about 6 per 100,000), reflecting the dramatic decline during this century in the occurrence of stomach cancer. Stomach cancer incidence among Japanese immigrants to the United States falls in succeeding generations. Incidence tends to be 1.5 to 2 times higher in men than in women. There is a progressive increase in incidence with increasing age.

ETIOLOGY. International variations and results of migrant studies strongly support a role of nongenetic factors in stomach cancer etiology. The actual causative factors, however, remain uncertain. The most promising explanation is that the diet may contain both carcinogenic and anticarcinogenic substances that influence stomach cells. Likely candidates for dietary carcinogens are (a) nitrosamines and (b) toxins produced by molds and bacteria in the course of food spoilage or pickling. Highly salted foods also appear to increase risk. Candidates for protective substances in the diet include vitamin C and beta-carotene, a vitamin A precursor. Nitrosamines are present in preserved or smoked foods and can be formed in the stomach through metabolism of naturally occurring nitrates and nitrites in food and water. Antioxidants, such as vitamin C, appear to inhibit nitrosamine formation. Although nitrosamines are potent carcinogens, their hypothesized role in the etiology of human stomach cancer remains unproven. Infection with *Helicobacter pylori* is a cause of gastritis and may predispose individuals to the carcinogenic effects of dietary nitrosamines.

TREATMENT. When detected early, stomach cancer may be treated by removal of all or part of the stomach. The great majority of patients are not candidates for this surgery either because the tumor has spread beyond the stomach or because they are too ill to withstand a major operative procedure. Other forms of cancer therapy such as radiation or drugs are not curative and have little palliative effect.

SCREENING. There is evidence, principally from Japan, that screening by barium x-ray studies, gastroscopy, or gastric cytology may detect stomach cancer at a stage when surgical cure is more likely. None of these techniques has had a rigorous

Table 21A-1. Estimated Crude Rates of Cancer by Site, Sex, and Region, 1980
(per 100,000 people)

	Africa		Latin America		China		Other Asia		All developing countries		All industrial countries	
Site or type of cancer	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Mouth/pharynx	6.2	3.7	8.7	3.3	6.1	4.4	15.2	8.3	10.5	5.9	14.7	4.4
Esophagus	3.0	1.1	5.8	2.2	21.0	12.3	4.9	3.5	9.6	5.6	7.3	2.9
Stomach	3.2	2.0	17.7	10.2	24.6	15.6	6.2	3.5	12.6	7.6	35.8	23.2
Colon/rectum	2.9	2.5	9.1	10.1	8.3	7.7	4.2	3.3	5.8	5.2	34.4	34.1
Liver	7.5	2.9	2.9	2.0	15.2	7.1	4.4	1.6	8.0	3.5	6.7	3.9
Lung	3.1	0.8	17.7	5.0	8.5	4.7	9.5	2.4	9.2	3.1	65.3	16.3
Breast	n.a.	12.3	n.a.	30.8	n.a.	6.4	n.a.	15.0	n.a.	13.8	n.a.	59.2
Cervix	n.a.	18.1	n.a.	27.0	n.a.	27.4	n.a.	20.0	n.a.	22.7	n.a.	16.4
Lymphoma	8.8	4.9	6.3	4.6	2.2	1.7	4.4	2.3	4.6	2.7	11.4	9.1
Leukemia	2.3	2.0	4.7	4.0	4.7	3.4	3.1	2.1	3.6	2.7	8.3	6.3
Other	31.7	26.3	57.4	48.1	35.4	18.3	27.0	22.1	33.5	24.5	108.8	83.0
Total	68.6	76.7	130.4	147.3	126.0	109.0	78.9	84.2	97.3	97.4	292.6	258.9

n.a. Not applicable.
Source: Parkin, Laara, and Muir 1988.

scientific evaluation (through a controlled clinical trial), so their actual value remains uncertain. In countries with high incidence and mortality from stomach cancer, the effectiveness of screening programs may be worth investigating. Stomach cancer does not occur with sufficient frequency in most populations, however, to justify mass screening activities. In these populations more selective screening of high-risk individuals may be practical if any screening measure is eventually proven to be effective in preventing stomach cancer death.

PREVENTION. Knowledge of risk factors is insufficient to recommend specific primary preventive strategies. In the industrial countries, particularly in North America, time trends in stomach cancer suggest a benefit from increased consumption of fresh fruits and vegetables and decreased consumption of spoiled foods or those preserved by pickling. Epidemiological data linking lowered risk to consumption of fresh fruits and vegetables (particularly those containing large amounts of vitamin C and beta-carotene) should be considered in discussions of national food policy. For example, it seems prudent to avoid strategies that discourage production and consumption of these foods.

Esophageal Cancer

Esophageal cancer arises from the cells lining the inside of the esophagus. The tumors may be either squamous cell or adenocarcinoma in histological appearance. Usual presenting symptoms are difficulty swallowing and steady chest pain. Diagnosis is made by barium x-ray studies or endoscopy. At diagnosis

Table 21A-2. New Cancer Incidence, by Site, Sex, and Region
(percent)

	Africa		Latin America		China		Other Asia		All developing countries		All industrial countries	
Site or type of cancer	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Mouth/pharynx	9.0	4.8	6.7	2.2	4.8	4.0	19.2	9.8	10.7	6.0	5.0	1.7
Esophagus	4.4	1.4	4.4	1.5	16.7	11.3	6.2	4.2	9.9	5.8	2.5	1.1
Stomach	4.6	2.6	13.6	6.9	19.5	14.3	7.8	4.2	12.9	7.8	12.2	9.0
Colon/rectum	4.2	3.2	7.0	6.9	6.6	7.1	5.3	3.9	5.9	5.4	11.7	13.2
Liver	11.0	3.7	2.2	1.3	12.1	6.5	5.6	1.9	8.2	3.6	2.3	1.5
Lung	4.5	1.0	13.6	3.4	6.7	4.3	12.1	2.9	9.4	3.2	22.3	6.3
Breast	n.a.	16.0	n.a.	20.9	n.a.	5.9	n.a.	17.8	n.a.	14.1	n.a.	22.9
Cervix	n.a.	23.7	n.a.	18.3	n.a.	25.1	n.a.	23.8	n.a.	23.3	n.a.	6.3
Lymphoma	12.8	6.4	4.9	3.1	1.7	1.6	5.6	2.7	4.7	2.8	3.9	3.5
Leukemia	3.3	2.6	3.6	2.7	3.7	3.1	3.9	2.5	3.7	2.8	2.8	2.4
Other	46.1	34.3	44.0	32.6	28.1	16.8	34.2	26.2	34.4	25.1	37.2	32.1

n.a. Not applicable.
Note: Figures reflect percentage of each cancer in the region.
Source: Parkin, Laara, and Muir 1988.

most esophageal cancers have spread into adjacent tissues. The prognosis is dismal, and fewer than 5 percent of patients survive for five years.

OCCURRENCE. Esophageal cancer accounts for approximately 310,000 new cases of cancer per year, four-fifths of which occur in the developing world. Esophageal cancer incidence and mortality rates vary greatly in different parts of the world. In the areas of Iran and the former Soviet Union which surround the Caspian Sea, mortality rates of more than 100 per 100,000 per year pertain for both men and women. Within North America the rate is less than 5 per 100,000 per year. The occurrence of esophageal cancer increases progressively with age. Rates tend to be about twice as high among men as women in most parts of the world, although in some areas of high incidence the male-female differences are less, whereas in others they are much greater. In the United States, esophageal cancer rates are higher among blacks than whites, and there appears to be a socioeconomic gradient, the disease being more frequent among the poor. Mortality rates for esophageal cancer, unlike those for stomach cancer, have not declined much in recent years in industrial countries.

ETIOLOGY. Tobacco and alcohol are the principal risk factors for esophageal cancer in industrial countries. The joint effect of these two substances in increasing risk appears to be greater than the sum of their individual effects. There is no clear explanation for the extremely high rates of esophageal cancer in areas such as the Caspian littoral and parts of northern China. Dietary characteristics have been implicated, but no particular component or habit has yet been proven to account for the highly elevated risk. Factors of interest include toxins in pickled foods and fermented drinks, carcinogens from burning tobacco or opium, and deficiencies in nutrients such as vitamin A, zinc, or selenium.

TREATMENT. Surgical resection offers the only chance of cure in localized disease, and surgery is also useful for relief of symptoms in more advanced cases. Radiation therapy may also relieve symptoms, particularly the inability to swallow.

SCREENING. The feasibility of screening for esophageal cancer has been considered in high-risk populations of northern China. Thus far, screening by endoscopy or cytology has not been shown to reduce mortality. This topic merits further study in areas of extremely high risk.

PREVENTION. In countries in which there is relatively low risk of esophageal cancer, the most reasonable primary preventive strategies are avoidance of tobacco and reduced consumption of alcoholic beverages. In countries with extraordinarily high rates of esophageal cancer, the actual risk factors have yet to be identified, so there is little information on which to base a primary prevention program. Studies of dietary supplementation with vitamins now being conducted in northern China may provide a better scientific basis for intervention.

Lung Cancer

Cancers of the lung may arise at any site in the respiratory tree beyond the trachea, but most of these tumors occur in small airways within the lung itself. There are four main histological subtypes: adenocarcinoma, squamous cell, small cell undifferentiated, and large cell undifferentiated. The relative frequency of these different histological types varies according to sex and exposure to cigarette smoking. Among nonsmokers, adenocarcinoma is most common. In smokers, squamous cell tumors are most common, although women smokers also have a high frequency of small cell undifferentiated cancers. The principal importance of histological type is that small cell undifferentiated tumors behave differently from the others. They are virtually always metastatic when diagnosed, and they are more responsive to combined chemotherapy and radiation. Initial symptoms of lung cancer are cough, bloody sputum, chest pain, or systemic symptoms of weight loss and fatigue. At least two-thirds of lung cancers have spread beyond the local site by the time of diagnosis. These tumors progress both by regional extension and distant metastases to the brain and other organs (this is particularly true for small cell undifferentiated tumors). About 90 percent of patients die within two years of diagnosis.

OCCURRENCE. Lung cancer accounts for approximately 660,000 new cases of cancer per year; just over 200,000 of these occur in developing countries. Countries with the highest mortality rates (for males) include the United Kingdom (about 115 deaths per 100,000 per year) and other countries of northern Europe and North America (about 75 deaths per 100,000 per year). Rates are lower in countries in which smoking is less common, such as Costa Rica (6 per 100,000) and Israel (25 per 100,000). In most countries mortality rates for females are approximately one-fifth to one-third those of males. Lung cancer incidence rates increase progressively with age except where cigarette smoking has been taken up more recently; in such countries relatively few older adults have smoked, so lung cancer rates are lower among the elderly. Incidence and mortality rates from lung cancer have increased dramatically in the past fifty years in many countries, and lung cancer has become the largest cause of cancer death in the world as a whole. The increases parallel (with a delay of at least twenty years) the uptake of tobacco smoking.

ETIOLOGY. The most important risk factor for lung cancer is cigarette smoking. Numerous studies have shown that smokers have ten to fifteen times the risk of lung cancer as nonsmokers. Among heavy smokers the risk is approximately twenty-five times that of nonsmokers. Risk is most closely related to the number of years a person has smoked. Filtered and low-tar cigarettes appear to be less risky than other types with regard to causing lung cancer (although they are not clearly less hazardous with respect to cardiovascular disease). In certain limited populations other risk factors are also important in lung cancer etiology. These include asbestos (related to mining and

industrial exposure), radon (principally related to underground mining but perhaps related to household exposures), and industrial exposure to substances such as bischloromethylether (BCME), nickel, and chromates. Dietary and serum studies show a decreased risk in persons eating large amounts of foods containing beta-carotene and in those with higher blood levels of this substance. The importance of these findings is uncertain.

TREATMENT. Surgical resection of lung cancer offers the only real chance of cure. Fewer than one-third of patients are candidates for this surgery, either because the tumor is no longer localized or because the patient is too unwell to withstand a major operation. Radiation therapy can palliate symptoms of lung cancer and, in some patients, may extend survival. A small fraction of patients with small cell undifferentiated tumors appear to have prolonged survival following intensive radiation or chemotherapy.

SCREENING. Various methods of early detection of lung cancer have been tested, but none has been shown to be effective. Methods tried include periodic chest radiographs and examination of sputum cytology. The principal problem with screening is that lung cancer progresses rapidly from the time when it is first detectable by screening methods to when it is no longer curable by surgery. Screening programs designed to increase this "window of opportunity" are under consideration and may eventually prove beneficial in selected groups of very high risk individuals.

PREVENTION. The principal preventive efforts are discouraging uptake of cigarette smoking and encouraging its discontinuance among those who already smoke. There is evidence that adult and teenage education can decrease use of cigarettes. More effective programs, however, will likely be aimed at restricting cigarette marketing (through prohibition of advertising) or sales (by heavy taxation). Efforts to portray cigarette smoking as antisocial behavior also may be effective in groups which are responsive to these social pressures. Reduction of occupational exposures to asbestos and other lung carcinogens is also warranted.

Liver Cancer

Most primary liver cancers are hepatocellular carcinomas (HCCs) and arise from hepatic parenchymal cells. Another important cell type is cholangiocarcinoma, which arises from the bile ducts. It accounts for fewer than 25 percent of all primary liver cancers in low-incidence areas and probably fewer than 10 percent in areas with high primary liver cancer incidence. Risk for cholangiocarcinoma appears to be increased in persons infected with *Clonorchis* and *Opisthorchis*, which are liver fluke infections prevalent in Southeast Asia and are acquired by eating uncooked fish. Within the developing world the great majority of liver cancers are HCCs, and the remainder of this discussion primarily focuses on that histological category. These tumors develop within the liver and cause localized destruction and enlargement of that organ. Presenting symptoms are abdominal mass, pain, and weight loss. The tumor tends to progress rapidly by local growth and extension. Distant metastases may occur but usually are not an important feature. Fewer than one person in twenty survives five years following diagnosis.

OCCURRENCE. Primary liver cancer accounts for 250,000 new cases of cancer per year; more than 190,000 of these occur in developing countries. Areas of highest incidence and mortality are in Sub-Saharan Africa and southern Asia. Rates tend to be lower in North America and western Europe. In Hong Kong, mortality rates for males are roughly 39 per 100,000; in the United States, they are less than 2 per 100,000. Mortality rates for females are generally one-half to one-quarter of the male rates. Substantial differences in rates occur for different ethnic groups within countries; for example, in the United States, ethnic Chinese have liver cancer rates approximately five to eight times those for whites. In countries of high incidence, liver cancer rates appear to plateau in middle adulthood, whereas in areas of low incidence they continue to rise progressively with age.

ETIOLOGY. There is compelling evidence from epidemiological and laboratory studies that hepatitis B virus can cause hepatocellular carcinoma. Liver cancer is most common in countries with high rates of HBV infection; the vast majority of patients with HCC have serological evidence of HBV infection, particularly the carrier state; and laboratory studies have shown viral DNA within hepatocellular carcinoma cells. In areas with high liver cancer incidence and mortality, HBV infection occurs early in life, probably during the perinatal period, and is spread from carrier mothers to their children. Other likely etiological factors include alcohol consumption and aflatoxin. In areas of low incidence, alcohol use and cirrhosis are usually (though not always) identified as risk factors in epidemiological studies; but in high incidence areas, alcohol is probably of minimal importance. In tropical Africa and Asia, food preservation is difficult, and growth of a mold (*Aspergillus flavus*) can contaminate foods with aflatoxins, which are strongly carcinogenic in laboratory animals. Epidemiological data support a higher risk of liver cancer in persons who consume relatively larger amounts of foods (particularly peanuts and grains) likely to be contaminated with aflatoxins. This factor appears to act jointly with hepatitis B virus in explaining much of the worldwide distribution of primary liver cancer. Other exposures (such as smoking) and hereditary disorders (such as hemochromatosis) are also associated with the risk of liver cancer, but these factors could only account for a small proportion of primary liver cancers in the developing countries.

TREATMENT. If detected very early, liver cancers can be surgically resected, although the procedure is a lengthy one and requires great surgical skill. Some patients have been treated

successfully with total resection of the liver and transplantation. Other treatment modalities, such as radiation and chemotherapy, are of little or no benefit for this condition.

SCREENING. Hepatocellular carcinomas produce alpha-fetoprotein, which can be detected by assay of peripheral blood. There are reports from uncontrolled studies in very high risk groups that alpha-fetoprotein screening detects asymptomatic persons who may be cured by surgical resection. The screening procedure has not, however, been the focus of any rigorous scientific study.

PREVENTION. In high-risk areas, preventive efforts are directed toward neonatal immunization with HBV vaccine. The effectiveness of this vaccine in preventing liver cancer has not been established, although current studies in China and the Gambia should eventually provide a better basis for assessing its value. Because of the strong evidence linking HBV infection to primary liver cancer, and because of the apparent safety of the vaccine, widespread programs of immunization are a prudent course of action until vaccine field trials have been completed. Other preventive efforts should focus on maintaining food stores, such as peanuts, under conditions that minimize growth of molds. Testing commercial food stores for aflatoxin is also a reasonable strategy. In areas endemic for liver fluke infection, control of these parasites may reduce cholangiocarcinoma occurrence.

Cervical Cancer

Cervical cancer arises in cells covering the lower, vaginal portion of the uterus. Progression from normal cells to cancerous ones appears to occur through phases of dysplasia, carcinoma in situ, and, finally, invasive cancer. Some terminology breaks down the preinvasive phases into three categories: cervical intraepithelial neoplasia I, II, and III. In most women, the transformation from normal cells to invasive carcinoma occurs over a long period (probably fifteen to thirty years), so there is long time when the condition can be detected at an early, noninvasive stage. In some women, however, the process appears to progress much more rapidly. Once cervical cancer becomes invasive it tends to spread by direct extension to the adjacent tissues of the pelvis and by metastases to distant sites such as the lung and liver. In the United States approximately 50 percent of invasive cervical cancers are still localized when detected. Approximately 80 percent of patients survive for five years if tumors are still localized and approximately 60 percent survive for five years through all stages. Most cervical cancers are found by screening examinations; however, symptoms of vaginal bleeding and pelvic pain occur if the disease progresses beyond the initial stage.

OCCURRENCE. Cancer of the cervix accounts for 470,000 new cases of cancer per year in the world. Approximately 80 percent of these occur in developing countries, where they cause about 155,000 deaths annually. Areas of highest incidence include Colombia (50 per 100,000) and Brazil (40 per 100,000); very low incidence is found among Israeli Jews (5 per 100,000). There is a strong socioeconomic gradient, the poorer countries and poorer groups of women within countries having the highest risk. Peak incidence of invasive cervical cancer occurs in late adulthood, and lower rates are observed in the elderly. In North America, cervical cancer mortality rates have declined dramatically during the past fifty years. This decline began before institution of Pap testing. Nevertheless, there is strong evidence from studies in the United States, Canada, and northern Europe that widespread use of the Pap test has contributed to the decline in mortality from this condition. In some countries of western Europe there has been a recent reversal of the trend toward falling rates, and cervical cancer appears to be increasing among younger women.

ETIOLOGY. Cervical cancer has many features of a sexually transmitted disease. Risks are highest among women who have had multiple sexual partners (or whose husbands have had multiple partners), who began sexual intercourse early in life, and who have sexual partners of lower socioeconomic status. Barrier methods of contraception appear protective; oral contraceptives increase risk moderately. Intensive efforts to identify an infectious cause of cervical cancer initially focused on herpes simplex virus 2 (HSV2). Indeed, cervical cancer risk is strongly associated with evidence of HSV2 infection, and laboratory studies have found HSV2 genetic material in cervical cancer cells. Nevertheless, more recent studies strongly suggest an etiological role for human papilloma virus (HPV), particularly types 16 and 18. This virus is more strongly associated with cervical cancer risk than is HSV2. Human papilloma virus causes benign growths (genital warts), and HPV DNA has been found intercalated in the human DNA of cervical cancer cells. Another risk factor is cigarette smoking. In most studies smokers have cervical cancer risks 1.5 to 2 times higher than nonsmokers. Although this association might be noncausal and due to the relationship between smoking and early sexual activity, the weight of evidence appears to favor a causal role for smoking in cervical cancer.

TREATMENT. Treatment of cervical neoplasia varies according to stage. For noninvasive lesions, initial destruction of the affected tissue by incision or laser and periodic follow-up may be all that is necessary to achieve a cure. As an alternative, hysterectomy removes the affected tissue and obviates any need for further surveillance. In more advanced disease the treatment options depend on the extent of tumor spread and the preferences of the patient. Extensive pelvic surgery and radiation are capable of curing disease which has spread beyond the cervix, although success in more advanced stages is less likely.

SCREENING. Pap testing involves cytological examination of cells scraped from the cervix and is the established screening method for cervical cancer. Properly performed, the Pap test is capable of detecting the vast majority of cervical neoplasms

before they become invasive. Positive tests require follow-up by repeat testing, biopsy, and, perhaps, culdoscopic examination to establish the diagnosis. Although annual Pap tests are recommended for high-risk women, less frequent testing (even as rarely as every five years) should be highly effective in reducing mortality. The principal obstacle in Pap test programs is that the women at highest risk are hard to reach because they are poor and avoid doctors. Failure to follow up positive or suspicious tests and unreliable cytology readings have also been problems in some programs. In most settings, highest priority should be assigned to achieving widespread acceptance of the Pap test program and to providing adequate definitive care. More frequent testing of already screened women is usually less important.

PREVENTION. No primary prevention programs have proven effective. The fact that cervical cancer is amenable to early detection and the lack of certainty about its etiology have directed public health efforts to screening. Some authors propose development and implementation of HPV vaccines, but these suggestions (like earlier suggestions for an HSV2 vaccine) appear to be premature.

Nasopharyngeal Cancer

Cancers of the oral cavity and pharynx fall into two relatively separate epidemiological categories. The first is nasopharyngeal cancer, which occurs principally among the populations of southern China and Southeast Asia. The second category, discussed separately below, includes other tumors of the mouth and pharynx, which occur with greatest frequency in people who habitually chew tobacco, betel, or similar substances.

Nasopharyngeal cancer arises in epithelial cells lining the surface of the nasopharynx. Usual presenting symptoms are lymph nodes in the neck; nasal bleeding and obstruction; symptoms of nerve compression, including headache; and earache or hearing loss. The five-year survival rate after treatment (radiotherapy) is approximately 22 to 35 percent.

OCCURRENCE. Although rare in most of the world, nasopharyngeal cancer is the most common cause of cancer death in some southern Chinese populations. Rates are high in areas with large groups of Chinese origin, as in Singapore and Malaysia. Nasopharyngeal cancer occurs with peak frequency among adults between the ages of thirty-five and sixty-five, but it also occurs relatively often in children and adolescents. Risk is somewhat higher in males than in females. The condition is associated with lower socioeconomic class in China and perhaps in other countries.

ETIOLOGY. The principal identified risk factors for nasopharyngeal cancer are Epstein-Barr virus infection and the consumption during infancy of traditionally prepared Chinese salted fish. The role of Epstein-Barr virus in this condition is unclear, because Epstein-Barr virus infection occurs throughout the world but nasopharyngeal cancer is seen principally in the Orient. Traditionally prepared Chinese salted fish contains carcinogens (perhaps volatile nitrosamines) which can produce nasopharyngeal tumors in rats. Volatile nitrosamines exist in other traditionally prepared foods in endemic areas, and further study of this issue may lead to an effective preventive strategy.

TREATMENT. Treatment of nasopharyngeal cancer involves high-dose radiation therapy. The tumor is generally responsive. Most patients achieve palliation and approximately one-quarter are cured.

SCREENING. There are no proven effective screening mechanisms for nasopharyngeal cancer.

PREVENTION. Primary prevention methods are speculative. Development of an Epstein-Barr virus vaccine has been proposed as a possible preventive method, but none has yet been developed, and the value of this method is uncertain. Changes in infant feeding practices (should the initial findings regarding salted fish and other foods be confirmed) appear to offer more promise for prevention.

Oral and Other Pharyngeal Cancers

Other cancers of the oral cavity and pharynx principally arise in the lining of the mouth and throat. Most of these tumors have a squamous cell histology. They typically present either as an oral ulcer or as enlarged lymph nodes in the neck, and they progress through local and regional extension rather than distant metastases. The usual outcome varies according to where the tumor arises within the mouth or pharynx. Cancers of the lip are generally found early and are cured by surgery. Those of the tongue or pharynx are approximately 70 percent fatal within five years.

OCCURRENCE. Worldwide, cancers of the mouth and pharynx account for more than 300,000 new cases of cancer per year, about two-thirds of which occur in developing economies. Incidence and mortality rates are highest in India, Hong Kong, Puerto Rico, Brazil, France, and Singapore. In most parts of the world, incidence rates are many times higher for males than for females. Rates increase progressively with age, and there is a strong socioeconomic gradient, the poorer people having higher rates.

ETIOLOGY. The principal risk factor for oral and pharyngeal cancers is tobacco smoking and chewing. In countries such as India, tobacco is often mixed with betel leaves, lime, and other substances. Chewing betel, or areca, nut may be a risk factor even in the absence of tobacco use. Cigarette smoking (especially reverse smoking) is also associated with risk. Other risk factors include alcohol consumption and lower intake of fruits and vegetables (which contain beta-carotene as well as other possible anticarcinogens). Cancers of the lip are strongly related to sunlight exposure.

TREATMENT. Treatment of these tumors principally involves surgery and radiation therapy. Surgery can be curative if tumors are found early, but it often results in substantial loss of function and requires intense rehabilitative efforts. Radiation therapy is used in conjunction with surgery and may contribute to survival. Radiation also may palliate patients with nonresectable tumors.

SCREENING. Although no screening programs have been proven to be effective, they appear likely to be beneficial. Examination of the mouth and pharynx of high-risk persons (perhaps linked to dental examinations) can detect many tumors before they have advanced to an untreatable stage. Oral examination also detects leukoplakia (white patches), a premalignant condition which requires close observation to monitor development of invasive cancer.

PREVENTION. Primary prevention should focus on reduced use of tobacco, either for chewing or smoking. Currently researchers are also investigating whether dietary supplementation, particularly with beta-carotene, can prevent oral and pharyngeal cancers. This notion remains to be proven.

Large Bowel Cancer

Cancers of the large bowel usually arise from the glandular epithelium and are classified histologically as adenocarcinomas. Most of these tumors appear to result from malignant transformation of benign adenomatous polyps. Tumors may arise anywhere in the large bowel; in the United States about three-quarters occur in the colon and one-quarter in the rectum. Although rectal and colonic cancers differ somewhat in their epidemiology and clinical behavior, they are considered together in this discussion. Large bowel cancers typically present as rectal bleeding, anemia, or signs of partial bowel obstruction. They tend to metastasize to regional lymph nodes and the liver, and about two-thirds have spread beyond the local stage by the time of diagnosis. About 50 percent of patients survive five years.

OCCURRENCE. Large bowel cancers cause more than 570,000 new cases of cancer in the world per year; about 30 percent of these occur in developing countries. Areas of greatest occurrence are the more westernized and industrialized countries. Mortality rates for males in New Zealand, Denmark, England, and Hungary range between 20 and 25 per 100,000. Typical areas of intermediate mortality are Greece (6 per 100,000) and Spain (11 per 100,000). The lowest rates are reported from less industrialized countries, such as Costa Rica (5 per 100,000) and Nigeria (probably below 2 per 100,000). Within areas of high incidence there are often populations with lower incidence. For example, in New Zealand, incidence rates in the Maori are approximately one-third those of the non-Maori. Incidence and mortality rates in women are generally about 20 percent lower than those in men. Risk increases progressively with age.

ETIOLOGY. The causes of large bowel cancer are unknown. International comparisons and migrant studies implicate dietary habits in the etiology of this disease. Dietary fat consumption is a strong candidate for a causal role, but the epidemiological data are inconclusive. Relative deficiency of vegetable fiber is also implicated in large bowel cancer etiology, particularly in persons with a high dietary fat intake. The risk of large bowel cancer is lower in people who consume large amounts of vegetables and fruit. Possible protective substances from these sources include vitamins C and E, beta-carotene, indoles, and the like. Adenomatous polyps and bowel cancers also appear to be at least partly determined genetically.

TREATMENT. Surgical resection of tumor and adjacent large bowel is curative if the cancer is detected early. For rectal cancer, radiation therapy may also contribute to the chance of cure and palliation. Chemotherapy of advanced lesions does not prolong survival materially, although some patients are improved by this treatment. Patients with rectal cancer often require a colostomy and need postoperative rehabilitation.

SCREENING. Although several screening practices have been broadly recommended for early detection of large bowel cancer, none has been conclusively shown to reduce mortality from this condition. Screening methods fall into three categories: stool occult blood testing, digital rectal examination, and sigmoidoscopic examination. Occult blood screening involves testing a small specimen of stool for the presence of hemoglobin. The test is easy to perform, inexpensive, and generally acceptable to patients. The principal problems with the test are that it results in a high number of false-positive findings, which require subsequent and (often costly) definitive diagnostic studies, and it has a relatively low sensitivity in the detection of small polyps and very early cancers (because these generally do not bleed). Large clinical trials of occult blood screening, despite involving tens of thousands of patients, have thus far failed to show a statistically significant reduction in large bowel cancer mortality associated with use of the test. It appears, therefore, that even if occult blood testing is effective, the magnitude of benefit is not large. A second method of screening is finger examination of the distal rectum; this can be performed at the time of a complete physical examination. Advantages of this screening method are simplicity and low cost. The primary disadvantage is that only a small proportion of large bowel cancers are potentially detectable in this way. The third screening method is visual examination of the rectum and sigmoid colon; this is best accomplished with a flexible sigmoidoscope. The procedure reliably detects early cancers and adenomatous polyps in the distal large bowel (usually the last 60 centimeters). Advantages of this procedure are that it appears to identify as many as 80 percent of persons who harbor polyps (although identification of all polyps in these people will require examination of the remainder of the large bowel by colonoscopy or contrast x-rays). Because polyp formers are the group at greatest risk of later developing bowel cancer, they should be kept under surveillance after being

identified by sigmoidoscopic examination. Disadvantages of the procedure are that it requires a skilled examiner (usually a physician, although trained nurses and paramedical personnel have been used successfully), the equipment is expensive, and the procedure entails more time and discomfort than other screening methods. Although flexible sigmoidoscopic screening has not yet been tested in a controlled clinical trial, on present evidence it appears to offer the best prospect for reducing colon cancer mortality.

PREVENTION. Uncertainty about the cause of large bowel cancer has largely prevented implementation of primary prevention programs. Dietary changes that include reduced fat and increased fiber intake have been recommended on the basis of epidemiological and laboratory data. The value of these interventions is largely a matter of conjecture, but it would be prudent for developing countries to resist dramatic changes away from their current high-fiber and low-fat diets.

Breast Cancer

The great majority (80 to 90 percent) of breast cancers arise from epithelial ductal cells; perhaps 10 percent are of lobular origin. The disease usually presents as a nodule or mass in the breast. Metastatic spread is common and may affect sites throughout the body. Involvement of the axillary lymph nodes is a usual feature of larger tumors. Other common sites of metastatic spread are the bones, liver, lung, and brain. Most breast cancers progress relatively slowly, and prolonged survival (several years) with active disease is common. After initial treatment the patients often follow a path of remission and relapse. In the United States approximately 70 percent of breast cancer patients survive five years. An important feature of breast cancer, unlike most other tumors, is that recurrence is common after a prolonged survival free of disease.

OCCURRENCE. There are approximately 575,000 new cases of breast cancer in the world each year; about 40 percent occur in developing countries. Areas of highest incidence include North America and western Europe (between 50 and 80 per 100,000), whereas incidence is lowest in Japan (about 20 per 100,000). Breast cancer incidence rates have been increasing in nearly all countries that have reliable data. The proportional increase has been greatest in areas of previously low incidence, such as Japan. Some of the increase in incidence in the United States, and perhaps elsewhere, is due to better detection of tumors. Breast cancer mortality rates in the United States have been relatively constant in the past fifty years. Mortality and incidence rates increase progressively with age until the time of menopause, after which point the rate of increase is less.

ETIOLOGY. Ionizing radiation is the only exogenous exposure that has been clearly shown to cause breast cancer. Nevertheless, several dietary and reproductive practices are related to breast cancer occurrence. Risk is increased in nulliparous women, and multiparity is associated with lower risk. Among women who have been pregnant, risk is highest in those who delayed pregnancy into their fourth decade. In most studies, earlier menarche and later menopause are associated with higher risk. A positive family history of breast cancer is also a risk factor. Increased consumption of dietary fat and calories is implicated in breast cancer etiology, but the epidemiological data are inconclusive. In general, women who are more obese have higher death rates from breast cancer, although it is not clear whether this is due to a greater risk of developing the disease or a greater risk of dying once it has occurred. Alcohol consumption also is implicated as a risk factor, particularly for high levels of consumption.

TREATMENT. Surgical resection of the tumor is the standard initial therapy for breast cancer. Surgery may remove only the tumor or, more commonly, the entire breast and associated axillary lymph nodes. Radiation therapy is often given to the breast and adjacent lymph nodes of women treated with simple excision. For an increasing proportion of women, primary treatment of breast cancer has come to include chemotherapy and hormonal therapy with Tamoxifen. There is strong evidence that these additional therapies lessen recurrence following surgery. Metastatic disease is treated with radiation or chemotherapy and hormonal therapy to reduce local symptoms and to induce remission. Many women with metastatic breast cancer respond well to treatment and have prolonged periods of normal function. In both industrial and developing countries Tamoxifen offers safe, inexpensive, and effective treatment.

SCREENING. There is conclusive evidence from randomized clinical trials that screening programs, consisting of mammography and physician examination of the breast, reduce breast cancer mortality by about 30 percent. The value of mammography alone is less certain. Hazards of screening are a small risk of cancer from radiation exposure and a risk of needless surgery generated by false-positive results. Of all cancers, however, evidence is strongest for a beneficial effect of screening in breast cancer.

PREVENTION. Epidemiological information on breast cancer is insufficient to support institution of any primary prevention program. The clearest risk factors relate to reproductive practices which are not readily amenable to preventive intervention. In fact, policies in developing countries are likely to emphasize reduced parity and delayed childbearing as ways to reduce population growth. These policies, if implemented successfully, are likely to increase breast cancer occurrence. Although several groups have recommended reduced dietary fat intake to control breast cancer, the epidemiological data do not consistently support this course of action. Most efforts at breast cancer control are now correctly directed toward earlier detection and improved treatment.

Lymphoma

These tumors arise from cells of the immune system, including lymphocytes, histiocytes, and their precursor cells. Lympho-

mas are a heterogeneous group of neoplasms which differ greatly in their epidemiology and clinical course. The reasons for including them in this chapter are (a) the Burkitt's lymphoma type occurs with great frequency in young children in parts of East Africa, (b) the Hodgkin's type tends to occur in children and in young adults during their productive years, and (c) both varieties are often cured by intensive therapy. Lymphoma usually presents as enlarged lymph nodes. Concomitant features include fever, weakness, loss of appetite, itching, and other symptoms of general illness. As it progresses it involves multiple sites in the body. Accordingly, lymphoma can produce a variety of complicating problems and usually causes death unless quickly treated.

OCCURRENCE. Lymphomas, considered as a group, account for approximately 135,000 new cases of cancer per year in the world; just over half of these occur in developing countries. Occurrence of different varieties of lymphoma varies from country to country. Burkitt's lymphoma occurs with highest frequency in parts of East Africa and New Guinea, where malaria is endemic. International patterns of Hodgkin's disease vary according to age group. Childhood Hodgkin's disease occurs most often in developing countries, whereas the disease in young adults is more common in northern Europe and North America. Both Hodgkin's disease and Burkitt's lymphoma affect males more often than females.

ETIOLOGY. Burkitt's lymphoma is strongly associated with Epstein-Barr virus infection in epidemiological and laboratory studies. The exact role of Epstein-Barr virus in causing Burkitt's lymphoma is uncertain, however. Areas with highest rates of Burkitt's lymphoma also have endemic malaria, and this geographic relationship has not been fully explained. Why should Epstein-Barr virus infection be associated with Burkitt's lymphoma in Africa and with nasopharyngeal cancer in China? Also, Epstein-Barr virus is a ubiquitous virus (it is the cause of infectious mononucleosis). What circumstances of infection or other factors are necessary for Burkitt's lymphoma, and how can they explain the dramatic geographic variations? These questions remain to be answered.

The cause of Hodgkin's disease is unknown, although some epidemiological data support an infectious etiology. The pattern of occurrence is in many ways consistent with the late effects of an early childhood infection. Thus far, however, no infectious agent has been identified. The causes of lymphomas other than Burkitt's lymphoma and Hodgkin's disease also are unknown. Patients on immunosuppressive therapy (for example, following organ transplantation) are at higher risk of lymphomas in the brain, but this is of relatively little importance to developing countries.

TREATMENT. Both Hodgkin's disease and Burkitt's lymphoma are highly responsive to therapy with radiation and chemotherapy. Many patients can be cured of Hodgkin's disease even if they have advanced disease. In early disease, cure may be achieved by radiation alone. More advanced disease requires intensive chemotherapy. African Burkitt's lymphoma also responds dramatically to chemotherapy, and more than 90 percent of patients achieve complete remission of their tumors. Perhaps 50 percent or more of them can be cured with currently available therapy.

SCREENING. There are no practical screening programs for lymphoma.

PREVENTION. Programs to control or eradicate malaria conceivably will decrease Burkitt's lymphoma. There is no good evidence, to date, that this occurs, however. Development of an Epstein-Barr virus vaccine has also been suggested as a preventive strategy for Burkitt's lymphoma. If an effective Epstein-Barr virus vaccine is developed, it logically should be tested in controlled trials for effectiveness in preventing Burkitt's lymphoma.

Leukemia

Leukemias are malignancies of the blood-forming cells. They are generally categorized according to the cell of origin and to whether the disease is chronic or acute in onset. The clinical behavior and treatment requirements differ for the various types of leukemia. We consider all leukemias together here because they often respond to treatment, and because the technological requirements for their treatment are similar. Leukemias are characterized by an overproduction of either mature (chronic leukemias) or immature (acute leukemias) bone marrow cells. Consequences of leukemia relate to deficiencies of normally functioning red cells, white cells, and platelets (necessary for control of bleeding). Accordingly, presenting symptoms of leukemia are anemia, loss of resistance to infection, or bruising and bleeding. Untreated, acute leukemias are rapidly fatal. Chronic leukemias may persist for years without causing debilitating symptoms. Alternatively, chronic myelogenous leukemia may enter an accelerated phase which mimics an acute leukemia and is rapidly fatal.

OCCURRENCE. Leukemias account for approximately 190,000 new cases of cancer per year worldwide. About 105,000 of these cases occur in developing countries. Leukemia incidence rates peak first in early childhood, decline, and then progressively rise again with age. Much of the childhood peak in leukemia is due to acute lymphocytic cell type, which is also highly responsive to intensive therapy. The adult leukemias are more often of the acute or chronic myelogenous varieties. International variations in leukemia incidence and mortality are not as pronounced as those for most other cancers, except that chronic lymphocytic leukemia is rarely seen in the Far East. Leukemia occurs more often in males than in females and in whites than in blacks or Asians.

ETIOLOGY. There is clear evidence from atomic bomb survivors in Japan and from other exposed groups that radiation causes acute leukemia. Increased leukemia rates are detectable within three years following acute radiation exposure, and the excess persists for decades. The increased risk is principally for

the myelocytic types. Other environmental exposures, including exposure to chemicals (particularly benzene), have been implicated as causes of leukemia. Alkylating drugs such as melphalan and busulfan, which are used in cancer chemotherapy, also can cause leukemia. For the vast majority of cases, however, there is no history of exposure to a known leukemogen other than normal background levels of radiation.

TREATMENT. Treatment of acute leukemias, particularly acute lymphocytic leukemia of childhood, has advanced dramatically in the past three decades. Intensive chemotherapy of acute lymphocytic leukemia appears capable of curing 50 percent of affected children. Treatment requires intensive medical support with close monitoring of chemotherapy side effects. Infectious complications are common. After an initial phase of induction therapy, children require prolonged periods of maintenance with intermittent chemotherapy. Adults with acute myelogenous leukemia require even more intensive therapy, but there is now the possibility of curing some of these patients. The chemotherapy regimens are intensely toxic to the normal bone marrow and other organs, and patients require close monitoring and support to treat complications of infection, bleeding, and anemia. Newer techniques of bone marrow transplantation, using either a closely matched donor or treated marrow cells from the patient, offer prospects for curing more leukemia patients. This therapy requires great technological sophistication and intense supportive care by medical and nursing personnel.

SCREENING. Acute leukemias progress very rapidly from the time at which they might be detectable by screening to the time of symptoms. There is no known value in treating chronic leukemias before they are symptomatic. For these two reasons, screening has no role in the management of these conditions.

PREVENTION. Avoiding unnecessary exposure to medical radiation is probably the most feasible approach to leukemia prevention. Other strategies include reduced occupational exposure to known leukemogens (such as benzene), and avoiding environmental contamination with these substances. These preventive strategies, even if effectively implemented, are unlikely to produce a measurable decrease in leukemia occurrence, because few cases are directly related to these factors.

Notes

We are indebted to Richard Doll, Kenneth Stanley, and Jan Stjernsward for their careful comments on earlier drafts. We have also benefited from discussions of this material at the World Health Organization and the United States Centers for Disease Control. The authors remain responsible for errors and conclusions. In particular, the conclusions do not necessarily reflect the views of the World Bank.

1. The use of aggregate numbers may obscure important differences between men and women. For most cancers, site specific incidence for men is about double that for women. Rates of cervical and breast cancer are sufficiently high in most of the developing world, however, that they nearly compensate for sex differences in other cancers and the overall rate of cancer in women is nearly equal to that of men. In tables 21A-1 and 21A-2 we give rates for men and women by main developing country region. Also refer to Parkin, Laara, and Muir (1988) for an excellent discussion of detailed rates.

2. Without any adjustment for price or cultural differences, an estimated relationship between 1982 manufactured cigarette consumption and income based on a cross-section sample of eighty-four countries is

$$cig/pop = 361 + 0.25\ \text{NNP}/pop - 0.000009\ (\text{NNP}/pop)^2 \quad R^2 = .56$$
$$(4.4)\ (5.9)\ (3.4)$$

At the mean per capita income ($3,500) for the sample the estimated income elasticity is 0.7. At incomes below $1,000 the income elasticity of cigarette consumption is above 1.3. The t-statistics are in parentheses (World Bank 1988; IARC 1986).

3. The purpose of using the percentage of per capita GNP, or %GNPN, rather than monetary units is to reduce measures of program costs across countries to approximately comparable units. The measure is deficient in that it primarily adjusts for labor cost differences between countries but does not account well for differences in foreign supply costs or in productivity. The deficiencies are offset, however, by the convenience of the measure.

4. The effect of increasing tobacco prices, for example, is greater in reducing consumption by the young than in reducing consumption among the currently addicted. Similarly, the costs of programs to convert present smokers to nonsmoking status can be high (Altman and others 1987).

5. After correcting nominal rates of interest for inflation, the real rate of interest has been in the vicinity of 3 percent in much of the world during the last twenty years.

6. Under exceptional circumstances and at very high cost, screening procedures appear to detect esophageal, stomach, or liver cancer at a stage at which early surgery may be successful. Research in Japan is under way on the practicality of endoscopy programs in areas of high stomach and esophageal cancer incidence.

7. Relative cancer survival is the survival probability for cancer patients in relation to that expected for persons of similar age in the general population.

8. Assuming an outpatient visit every fourteen days at $1.50 per visit, the cost of aspirin or paracetamol is $0.10 per day, the cost of codeine is $1.00 per day and the cost of morphine is $0.20 per day. For severe symptoms it is assumed that there would be forty-five days during which codeine and paracetamol were required and forty-five days during which morphine was needed.

References

Altman, D. G., J. A. Flora, S. P. Fortman, and J. W. Farquhar. 1987. "The Cost Effectiveness of Three Smoking Cessation Programs." *American Journal of Public Health* 77(2):162–65.

American Cancer Society. 1987. "Cancer: Basic Data." In *Cancer Facts and Figures—1987*. American Cancer Society: Atlanta, Ga.

Axtell, L. M., A. J. Asire, and M. H. Myers. 1976. *Cancer Patient Survival*. Report 5. U.S. Department of Health, Education, and Welfare; National Cancer Institute, Washington, D.C.

Bailar, John, III, and Elaine M. Smith. 1986. "Progress against Cancer?" *New England Journal of Medicine* 314:1226–32.

Baines C. J., A. B. Miller, and A. A. Bassett. 1989. "Physical Examination: Its Role as a Single Screening Modality in the Canadian National Breast Screening Study." *Cancer* 63:1816–22.

Barnum, H. 1988. "Economic Issues in Planning the Use of Health Resources for Chronic Diseases in China." Background Document for World Bank Sector Review, Population, Health, and Nutrition Department. Washington, D.C.

Beasley, R. Palmer. 1988. "Hepatitis B Immunization Strategies." WHO/EPI/GEN/88.5. World Health Organization/Expanded Programme on Immunization, Geneva.

Beasley, R. Palmer, Chia-Chin Lin, Lu-Yu Hwang, and Chia-Siang Chien. 1981. "Hepatocellular Carcinoma and Hepatitis B Virus." *Lancet* November 21, 1129–33.

Bhargava, M. Krishna. N.d. *Karnataka State Cancer Control Programme*. Kidwai Memorial Institute of Oncology, Bangalore.

Bjelke, E. 1982. "The Recession of Stomach Cancer: Selected Aspects." In K. Magnus, ed., *Trends in Cancer Incidence*. Washington, D.C.: Hemisphere Publishing.

Boyle, P., D. G. Zaridze, and M. Smans. 1985. "Descriptive Epidemiology of Colorectal Cancer." *International Journal of Cancer* 36:9–18.

Bulatao-Jayme, J., E. M. Almero, C. A. Castro, T. R. Jardeleza, and L. A. Salamat. 1982. "A Case-Control Dietary Study of Primary Liver Cancer Risk from Aflatoxin Exposure." *International Journal of Epidemiology* 11:112–19.

Bumgarner, J. Richard, ed. 1992. *China: Long-Term Issues and Options in the Health Transition*. A World Bank Country Study. Washington, D.C.

Byers, T. 1988. "Diet and Cancer. Any Progress in the Interim?" *Cancer* 62:1713–24.

Chamberlain, J., N. E. Day, M. Hakama, A. B. Miller, and P. Prorok. 1986. "UICC (Union International Contre le Cancer [International Union against Cancer]) Workshop on Evaluation of Screening Programmes for Gastrointestinal Cancer." *International Journal of Cancer* 37:329–34.

Clayman, C. B. 1989. "Mass Screening for Colorectal Cancer: Are We Ready?" *JAMA* 261(4):609.

Correa, P. 1992. "Human Gastric Carcinogenesis: A Multistep and Multifunctional Process." *Cancer Research* 52:6735–40.

Cramer, D. W. 1982. "Uterine Cervix." In Schottenfeld and Fraumeni, Jr., eds., *Cancer Epidemiology and Prevention*. Philadelphia: W. B. Saunders.

Crofton, J. 1984. "The Gathering Smoke Clouds: A Worldwide Challenge." *International Journal of Epidemiology* 13:269–70.

Cromwell, J., and P. Gertman. 1979. "The Cost of Cancer." *Laryngoscope* 89:393–409.

Dahl, June, and David Joranson. 1987. "Relieving Cancer Pain." *World Health* 11:28–29.

Day, N. E., C. J. Baines, J. Chamberlain, M. Hakama, A. B. Miller, and P. Prorok. 1986. "UICC (Union International Contre le Cancer [International Union against Cancer]) Project on Screening for Cancer: Report of the Workshop on Screening for Breast Cancer." *International Journal of Cancer* 38:303–8.

Doll, Richard, and Richard Peto. 1981. *The Causes of Cancer: Quantitative Estimates of Avoidable Risks of Cancer in the United States Today*. Oxford: Oxford University Press.

Eddy, David M. 1981. "The Economics of Cancer Prevention and Detection." *Cancer* 47:1200–09.

———. 1986a. *A Computer-Based Model for Designing Cancer Control Strategies*. NCI Monographs 64(2):74–82.

———. 1986b. "Secondary Prevention of Cancer: An Overview." *Bulletin of the World Health Organization* 64(3):421–29.

Eddy, David M., and Michael Schwartz. 1982. "Mathematical Models in Screening." In David Schottenfeld and Joseph Fraumeni, Jr., eds., *Cancer Epidemiology and Prevention*. London: W. B. Saunders Company.

Editorial Committee for the Atlas of Cancer Mortality, eds. 1976. *Atlas of Cancer Mortality in the People's Republic of China*. Beijing National Cancer Control Office of the Ministry of Health.

Feinstein, A. R., D. M. Sosin, and C. K. Wells. 1985. "The Will Rogers Phenomenon: Stage Migration and New Diagnostic Techniques as a Source of Misleading Statistics for Survival in Cancer." *New England Journal of Medicine* 312:1604–8.

Fleischer, D. E., S. B. Goldberg, T. H. Browning, J. N. Cooper, E. Friedman, F. H. Goldner, E. B. Keeffe, and L. E. Smith. 1989. "Detection and Surveillance of Colorectal Cancer." *JAMA* 261:580–85.

Francis D. P., S. C. Hadler, S. E. Thompson, J. C. Maynard, D. G. Ostrow, N. Altman, E. H. Braff, P. O'Malley, D. Hawkins, F. N. Judson, K. Penley, T. Nylund, G. Christie, F. Meyers, J. N. Moore, Jr., A. Gardner, I. L. Doto, J. H. Miller, G. H. Reynolds, B. L. Murphy, C. A. Schable, B. T. Clark, J. W. Curran, and A. G. Redeker. 1982. "The Prevention of Hepatitis B with Vaccine: Report of the Centers for Disease Control Multi-Center Efficacy Trial among Homosexual Men." *Annals of Internal Medicine* 97(3):362–66.

Gambia Hepatitis Study Group. 1989. "Hepatitis B Vaccine in the Expanded Programme of Immunization: The Gambian Experience." *Lancet* May 13:1057–60.

Ghadirian, P., J. P. Thouez, and A. Simard. 1988. "La géographie du cancer de l'oesophage." *Social Science and Medicine* 27:971–85.

Gray, Nigel. 1985. "Cancer Risks and Cancer Prevention in the Third World." In M. P. Vessey and M. Gray, eds., *Cancer Risks and Prevention*. Oxford: Oxford University Press.

Greenwald, P., and E. J. Sondik, eds. 1986. "Cancer Control Objectives for the Nation: 1985–2000." NCI Monographs 2. National Cancer Institute, Washington, D.C.

Hakulinen, T., H. Hansluwka, A. D. Lopez, and T. Nakada. 1986. "Global and Regional Mortality Patterns by Cause of Death in 1980." *International Journal of Epidemiology* 15:227–33.

Hanley, James A. 1986. "Evaluating Primary Prevention Programmes Against Cancer." *Bulletin of the World Health Organization* 64(2):311–20.

Hartunian, Nelson, Charles N. Smart, and Mark Thompson. 1980. "The Incidence of Economic Costs of Cancer, Motor Vehicle Injuries, Coronary Heart Disease, and Stroke: A Comparative Analysis." *Public Health* 70(12):1249–60.

Hodgson, Thomas. 1988. "Annual Costs of Illness Versus Lifetime Costs of Illness and Implications of Structural Change." *Drug Information Journal* 22:323–41.

Hsu, Hsu-Mei, Ding-Shinn Chen, Cheng-Hua Chuang, Joseph Chih-Feng Lu, De-Min Jebo, Chin-Chang Lee, Hsing-Chi Lu, Shih-Hsiung Chen, Yue-Fen Wang, Chinying Chen Wang, Kwang-Juei Lo, Chun-Jen Shih, and Juei-Low Sung. 1988. "Efficacy of a Mass Hepatitis B Vaccination Program in Taiwan." JAMA 260:2231–35.

IARC (International Agency for Research on Cancer). 1986. *Tobacco Smoking*. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans 38. Lyons.

IARC (International Agency for Research on Cancer) Working Group on Evaluation of Cervical Cancer Screening Programmes. 1986. "Screening for Squamous Cervical Cancer: Duration of Low Risk after Negative Results of Cervical Cytology and Its Implication for Screening Policies." *British Medical Journal* 293:659–64.

India, Ministry of Health and Family Welfare. 1984. *National Cancer Control Programme for India*. Directorate General of Health Services, New Delhi.

ITFH (International Task Force on Hepatitis B Immunization). 1988. *Notes on Hepatitis B and Its Control*. PATH (Program for Appropriate Technology in Health.) Seattle, Wash. Published report.

Kelsey, J. L., and N. G. Hildreth. 1983. *Breast and Gynecologic Cancer Epidemiology*. Boca Raton, Fla.: CRC Press.

Knight, K. K., J. E. Fielding, and R. N. Battista. 1989. "Occult Blood Screening for Colorectal Cancer." *JAMA* 261:587–93.

Knox, E. G. 1982. "Cancer of the Uterine Cervix." In K. Magnus, ed., *Trends in Cancer Incidence*. Washington, D.C.: Hemisphere Publishing.

Kristein, M. M., C. B. Arnold, and E. L. Wynder. 1977. "Health Economics and Preventive Care." *Science* 195(4277):457–62.

Kurihara, Minoru, Kunio Aoki, and Suketami Tominaga. 1984. *Cancer Mortality Statistics in the World*. Nagoya, Japan: University of Nagoya Press.

Lew, E. A., and L. Garfinkel. 1979. "Variations in Mortality by Weight among 750,000 Men and Women." *Journal of Chronic Diseases* 32(8):563–76.

Luce, B. R. 1980. "Allocating Costs and Benefits in Disease Prevention Programs: An Application to Cervical Cancer Screening." Case Study 7. U.S. Congress, Office of Technology Assessment, Washington, D.C.

Lynge, E., M. Madsen, and G. Engholm. 1989. "Effect of Organized Screening on Incidence and Mortality of Cervical Cancer in Denmark." *Cancer Research* 49:2157–60.

Mackay, Judith. 1989. "Battlefield for the Tobacco War." JAMA 261:28–29.

McMichael, A. J. 1984. "Oral Cancer in the Third World: Time for Preventive Intervention?" *International Journal of Epidemiology* 13:403–5.

Maynard, J. E., M. A. Kane, M. J. Alter, and S. C. Hadler. 1988. "Control of Hepatitis B by Immunization." *Viral Hepatitis and Liver Disease*. New York: Alan R. Liss.

Miller, R. W., and F. W. McKay. 1984. "Decline in the U.S. Childhood Cancer Mortality: 1950 through 1980." *JAMA* 251:1567–70.

Muir, C. S., and J. Nectoux. 1982. "International Patterns of Cancer." In D. Schottenfeld and J. F. Fraumeni, Jr., eds., *Cancer Epidemiology and Prevention*. Pennsylvania: W. B. Saunders.

Muir, C. S., J. Waterhouse, R. Mack, J. Powell, and S. Whelan. 1988. *Cancer Incidence in Five Continents*. Scientific Publication 88. Lyons: International Agency for Research on Cancer.

Nair, M. Krishnan. 1988. *Ten-Year Action Plan for Cancer Control in Kerala*. Printed at St. Joseph's Press, Trivandrum. Approved by the State Cancer Control Advisory Board of Kerala. Jointly published by the Regional Cancer Centre, Trivandrum and the Cancer Unit, World Health Organization, Geneva.

National Research Council, Committee on Diet, Nutrition, and Cancer. 1982. *Diet, Nutrition, and Cancer*. Washington, D.C.: National Academy Press.

NIH (National Institutes of Health). 1988. *1987 Annual Cancer Statistics Review*. NIH Publication 88-2789, National Cancer Institute, Division of Cancer Prevention and Control. U.S. Department of Health and Human Services. Bethesda, Md.

Parkin, D. M. 1985. "A Computer Simulation Model for the Practical Planning of Cervical Cancer Screening Programmes." *British Journal of Cancer* 51:551–68.

———, ed. *Cancer Occurrence in Developing Countries*. Scientific Publication 75. Lyons: International Agency for Research on Cancer.

Parkin, D. M., E. Laara, and C. S. Muir. 1988. "Estimates of the Worldwide Frequency of Sixteen Major Cancers in 1980." *International Journal of Cancer* 41:184–97.

Parkin, D. M., and S. M. Moss. 1986. "An Evaluation of Screening Policies for Cervical Cancer in England and Wales Using a Computer Simulation Model." *Journal of Epidemiological and Community Health* 40(2):143–53.

Percy, C., and C. S. Muir. 1989. "The International Comparability of Cancer Mortality Data: Results of an International Death Certificate Study." *American Journal of Epidemiology* 129:934–46.

Peto, Richard. 1986. "Influence of Dose and Duration of Smoking on Lung Cancer Rates." In D. G. Zaridze and Richard Peto, eds., *Tobacco: A Major International Health Hazard*. Scientific Publication 74. Lyons: International Agency for Research on Cancer.

Poirier, S., H. Ohshima, G. De-The, A. Hubert, M. C. Bourgade, and H. Bartsch. 1987. "Volatile Nitrosamine Levels in Common Foods from Tunisia, South China, and Greenland: High-Risk Areas for Nasopharyngeal Carcinoma (NPC)." *International Journal of Cancer* 39:293–96.

Portenoy, Russell K. 1988. "Practical Aspects of Pain Control in the Patient with Cancer." *Ca-A Cancer Journal for Clinicians* 38(6):327–52.

Rice, D. P., and T. A. Hodgson. 1981. *Social and Economic Implications of Cancer in the United States of America*. Publication (PHS) 81-1404. U.S. Department of Health and Human Services, Washington, D.C.

Rice, D. P., T. A. Hodgson, and A. N. Kopstein. 1985. "The Economic Costs of Illness: A Replication and Update." *Health Care Financing Review* 7(1):61–80.

Schottenfeld, D., and J. F. Fraumeni, Jr. 1982. *Cancer Epidemiology and Prevention*. Philadelphia: W. B. Saunders.

Schwartz, M. 1978. "An Analysis of the Benefits of Serial Screening for Breast Cancer Based on a Mathematical Model of the Disease." *Cancer* 51:1550–64.

Schweitzer, Stuart. 1977. "Cost Effectiveness of Early Detection of Disease." *Health Services Research* 9(1):22–32.

Scotto, Joseph, and Leonard Chiazze. 1976. "Third National Cancer Survey: Hospitalizations and Payments to Hospitals." DHEW Publication 76-1094. Department of Health, Education, and Welfare, Washington, D.C.

Segi, Mitsuo, Suketami Tominaga, Kunio Aoki, and Isaburo Fujimoto, eds. 1981. *Cancer Mortality and Morbidity Statistics: Japan and the World*. GANN Monograph on Cancer Research 26. Tokyo: Japan Scientific Societies Press. Published report.

Shapiro, S., W. Venet, P. Strax, L. Venet, and R. Roeser. 1982. "Ten to Fourteen Year Effect of Screening on Breast Cancer Mortality." *Journal of the National Cancer Institute* 69(2):349–55.

Silverberg, E. and J. Lubera. 1987. "Cancer Statistics 1987." *Ca-A Cancer Journal for Clinicians*. 37(1)2–19.

Simopoulos, A. P. 1987. "Obesity and Carcinogenesis: Historical Perspective." *American Journal of Clinical Nutrition* 45:271–76.

Stanley, K. 1986. "Lung Cancer and Tobacco—A Global Problem." *Cancer Detection and Prevention* 9:83–89.

Stanley, K., J. Stjernsward, and V. Koroltchouk. 1988. "Cancers of the Stomach, Lung, and Breast: Mortality Trends and Control Strategies." *World Health Statistics Quarterly* 41:107–14.

Stjernsward, J. 1988. "WHO Cancer Pain Relief Programme." *Cancer Surveys* 7(1):195–208.

———. 1990. "National Training of Radiotherapists in Sri Lanka and Zimbabwe: Priorities and Strategies for Cancer Control in Developing Countries." *International Journal of Radiation Oncology and Biological Physics* 19(5):001–4.

Stjernsward, J., K. Stanley, David M. Eddy, M. Tsechkovski, L. Sobin, I. Koza, and K. H. Notaney. 1985. "Cancer Control: Strategies and Priorities." *World Health Forum* 6:160–64.

Sun Tsung-Tang, Chu Yuan-Rong, Ni Zhi-Quan, Lu Jian-Hua, Huang Fei, Ni Zheng-Ping, Pei Xu-Fang, Yu Zhi-Ian, and Liu Guo-Ting. 1986. "A Pilot Study on Universal Immunization of Newborn Infants in an Area of Hepatitis B Virus and Primary Hepatocellular Carcinoma Prevalence with a Low Dose of Hepatitis B Vaccine." *Journal of Cellular Physiology* 4(supplement):83–90.

Szmuness, W., C. E. Stevens, E. A. Zang, E. J. Harley, and A. Kellner. 1981. "A Controlled Clinical Trial of the Efficacy of the Hepatitis B Vaccine (Heptavax B): A Final Report." *Hepatology* 1:377–85.

Tabar, L., C. J. Fagerberg, A. Gad, L. Baldetorp, L. H. Holmberg, O. Grontoft, U. Ljungquist, B. Lundstrom, J. C. Manson, and G. Eklund. 1985. "Reduction in Mortality from Breast Cancer after Mass Screening with Mammography." *Lancet* 1(8433):829–32.

Takenaga, Nobuyuki, Ichiro Kai, and Gen Ohi. 1985. "Evaluation of Three Cervical Cancer Detection Programs in Japan with Special Reference to Cost-Benefit Analysis." *Cancer* 55(10):2514–19.

Thorn, Jennifer B., J. Elizabeth MacGregor, Elizabeth M. Russell, and Kathleen Swanson. 1975. "Costs of Detecting and Treating Cancer of the Uterine Cervix in North-East Scotland in 1971." *Lancet* March 22 674–76.

USDHHS (U.S. Department of Health and Human Services). 1977. *Cancer Patient Survival*. Report 5. DHEW Publication NIH (National Institutes of Health) 77–992. Department of Health, Education, and Welfare; Washington, D.C.

———. 1982. *The Health Consequences of Smoking:* CANCER. Report of the Surgeon General. Public Health Service, Office of Smoking and Health, Washington, D.C.

———. 1988. *1987 Annual Cancer Statistics Review, Including Cancer Trends: 1950–1985*. NIH (National Institutes of Health) Publication 88-2789. National Cancer Institute, Washington, D.C.

Van Rensburg, S. J., P. Cook-Mozaffari, D. J. Van Schalkwyk, J. J. Van Der Watt, T. J. Vincent, and I. F. Purchase. 1985. "Hepatocellular Carcinoma and Dietary Aflatoxin in Mozambique and Transkei." *British Journal of Cancer* 51:713–26.

Wainwright, R. B., B. J. McMahon, L. R. Bulkow, D. B. Hall, M. A. Fitzgerald, A. P. Harpster, S. C. Hadler, A. P. Lanier, and W. L. Heyward. 1989. "Duration of Immunogenicity and Efficacy of Hepatitis B Vaccine in a Yupik Eskimo Population." JAMA 261:2362–66.

Warnakulasuriya, K. A. A. S., A. N. I. Ekanayake, S. Sivayoham, J. Stjernsward, J. J. Pindborg, L. H. Sobin, and K. S. G. P. Perera. 1984. "Utilization of Primary Health Care Workers for Early Detection of Oral Cancer and Precancer Cases in Sri Lanka." *Bulletin of the World Health Organization* 62(2):243–50.

Warner, Kenneth. 1987. "Health and Economic Implications of a Tobacco Free Society." JAMA 258:2080–86.

Waterhouse, J., C. S. Muir, P. Correa, and J. Powell, eds. 1976. *Cancer Incidence in Five Continents*. Vol. 3. Scientific Publication 15. Lyons: International Agency for Research on Cancer.

Waterhouse, J., C. S. Muir, K. Shanmugaratnam, and J. Powell, eds. 1982. *Cancer Incidence in Five Continents*. Vol. 4. Scientific Publication 42. Lyons: International Agency for Research on Cancer.

Widjaya, A. 1988. "Cost Effective Analysis in Various Hepatitis B Virus Control Programs in Indonesia." Department of Health, Centre for Laboratory Services, Jakarta.

Willett, W. S., and B. MacMahon. 1984. "Diet and Cancer—An Overview (Parts 1 and 2)." *New England Journal of Medicine* 310:633–38.

World Bank. 1988. *World Development Report 1988*. Washington, D.C.: Oxford University Press.

WHO (World Health Organization). 1983. "Prevention of Liver Cancer." Technical Report 691. Geneva.

———. 1984. "Control of Oral Cancer in Developing Countries." *Bulletin of the World Health Organization* 62(6):817–30.

———. 1985. "Essential Drugs for Cancer Chemotherapy: Memorandum from a WHO Meeting." *Bulletin of the World Health Organization* 63(6): 999–1002.

———. 1986a. *Cancer Pain Relief*. WHO Monograph. Geneva.

———. 1986b. "Control of Cancer of the Cervix: A WHO Meeting." *Bulletin of the World Health Organization* 64(4):607–18.

———. 1986c. "The Use of Quantitative Methods in Planning National Cancer Control Programmes." *Bulletin of the World Health Organization* 64(5):683–93.

———. 1988a. "General Strategies and Provisions for Cancer Control in Chile." CAN/88.1. Geneva.

———. 1988b. "Global Medium-Term Programme for the WHO Cancer Control Programme during the Period 1990–1995." CAN/MTP/88.1. Geneva.

———. 1990. "Diet, Nutrition, and Prevention of Chronic Diseases." Technical Report. Geneva.

WHO (World Health Organization)/Indonesia, Ministry of Health. 1989. *National Cancer Control Program in Indonesia*. Geneva.

Yeh, F.-S., M. C. Yu, C.-C. Mo, S. Luo, M. J. Tong, and B. E. Henderson. 1989. "Hepatitis B Virus, Aflatoxins, and Hepatocellular Carcinoma in Southern Guangxi, China." *Cancer Research* 49:2506–9.

Yu, M. C., J. H. C. Ho, S.-H. Lai, and B. E. Henderson. 1986. "Cantonese-Style Salted Fish as a Cause of Nasopharyngeal Carcinoma: Report of a Case-Control Study in Hong Kong." *Cancer Research* 46:956–61.

Source: Dean T. Jamison, W. Henry Mosley, Anthony R. Measham, and Jose Luis Bobadilla (eds.). *Disease Control Priorities in Developing Countries*. New York: Oxford University Press for the World Bank. 1993.